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Synthesis and Antiviral Activity of Novel Spirocyclic Nucleosides

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The synthesis of a number of spirocyclic ribonucleosides containing either a triazolic or azetidinic system is described, along with two analogous phosphonate derivatives of the former. These systems were constructed from the same β -D-psicofuranose starting material. The triazole spirocyclic nucleosides were constructed using the 1-azido-1-hydroxymethyl derived sugars, where the primary alcohol was alkylated with a range of propargyl bromides, whereas the azetidine systems originated from the corresponding 1-cyano-1-hydroxymethyl sugars. Owing to their close similarity with ribavirin, the library of compounds were investigated for their antiviral properties using MHV (Mouse Hepatitis Virus) as a model.

1. Introduction

Ribavirin **1** (also known as rebatol[®] and virazole[®]), a 1,2,4-triazole nucleoside, discovered by Witkowski and co-workers in 1972,¹ exhibits a broad spectrum of antiviral activity against both DNA and RNA viruses and has been used for the treatment of a variety of viral infections, such as severe respiratory syncytial virus (RSV) infection, lassa fever, influenza A and B, measles and mumps.² Today ribavirin is the standard care for the treatment of chronic hepatitis C in combination with PEGylated interferon- α .³

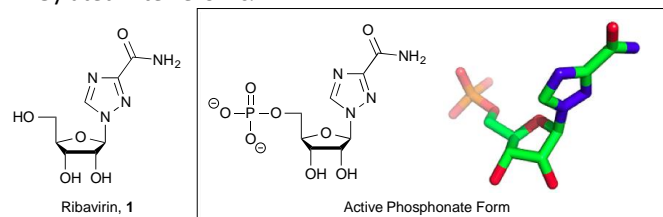


Figure 1 : Ribavirin **1**, and its phosphorylated active form.

Despite its potent antiviral activity, the use of ribavirin is limited by adverse effects - mainly associated with haemolytic anaemia.⁴ In plasma, the nucleoside is transported into

erythrocytes by suitable transporters and converted into its phosphate forms (RMP, RDP and RTP). These then accumulate owing to the lack the phosphatases needed to hydrolyse them, leading to a relative deficiency of adenosine triphosphate and subsequent extravascular haemolysis.⁵

Therefore, driven by the need to find safer and more specific IMP mimics, we set out to develop a range of spirocyclic nucleosides, the first class containing a [1,2,3]-triazolyl moiety (accessed via an intramolecular [1,3]-dipolar cycloaddition) and the second an azetidine functionality (accessed *via* intramolecular S_N2 reaction) around the spirocyclic anomeric centre (Figure 2) and which show remarkable structural similarity to ribavirin. Nucleosides where the conformational restriction involves the nucleobase are known as *cyclonucleosides*, and have garnered interest on a number of fronts, including agrochemical (e.g. hydantocidin),⁶ as well as being of synthetic interest.^{7,8}

Nucleosides restricted in this way can often show a greater specificity towards their enzymatic target, and this can result in enhanced biological activity.⁹

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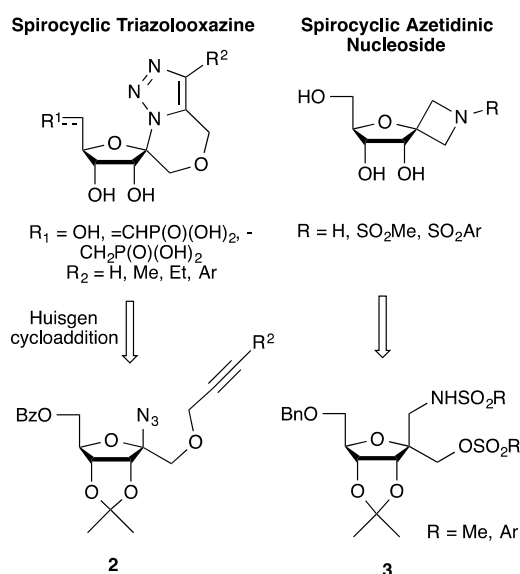


Figure 2: Spirocyclic nucleosides targeted

2. Results and Discussion

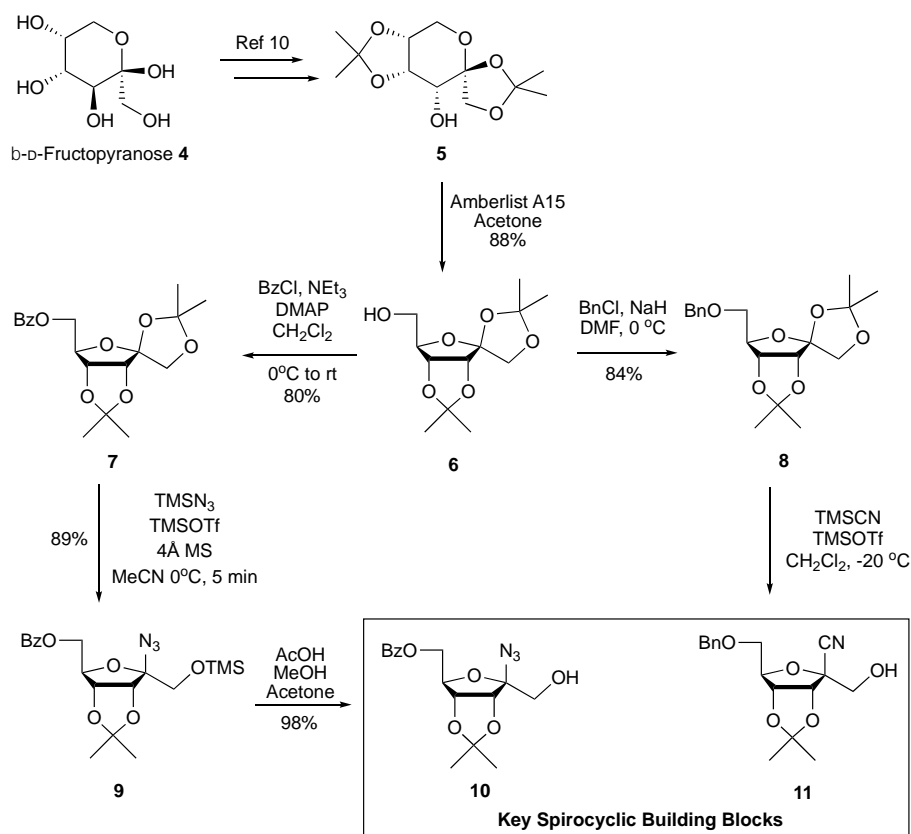
The starting point for the synthesis of both spirocyclic systems was β -D-fructopyranose **4**, which was converted to D-

psicopyranose **5** in a straightforward and previously reported three step procedure.¹⁰ This intermediate was then converted to the corresponding furanose **6** using amberlyst A15 resin in acetone (Scheme 1). The subsequent protecting group used on the 6'OH-position was found to be hugely influential on the next glycosidation step. In the case of azide insertion, the benzoate ester **7** sufficed, but for the nitrile insertion, the benzylated intermediate **8** was required for efficient reaction (Scheme 1). These glycosidations were achieved through the use of trimethylsilyl triflate and either TMS azide for compound **9**, or TMS nitrile for compound **11**.¹¹

The former resulted in the trimethylsilyl ether which required acidic methanolysis to give the primary alcohol **10**, but fortunately this was very high yielding. Also satisfyingly, only the desired anomer was produced and this is assumed to be a result of the intermediate oxonium ion being very hindered on the α -face owing to the presence of the acetonide, in addition to the product being the more stable isomer owing to a positive anomeric effect.

2.1 [1,2,3]-Triazolooxazines

With building block **10** in hand, the alkylation of the primary alcohol to form the alkynyl-azido compound **2** was undertaken. A variety of bases were used to achieve this, initially with propargyl bromide as the electrophile (Table 1). Using sodium hydride in THF (Entry 1), two products were isolated

Scheme 1 : Access to psicofuranosyl derivatives building blocks **10** and **11**.

The first was identified as the required product **2a**, which was obtained in a disappointing 11% yield, and the second – obtained in 6% yield – was the hydrolysed diol **12**. None of the other metal bases screened gave the desired compound in any useful yield, and interestingly KHMDS in THF gave predominantly the diol **12**. We then tested the non-metallic phosphazene base BEMP in acetonitrile (Entry 6), and pleasingly this gave exclusively the azido-alkynyl product **2a** in 54% yield.

Table 1 : Alkylation study for the synthesis of azido-alkyne **2a**.

Entry	Base	Solvent	Yield 2a (%)	Yield 12 (%)
1	NaH	THF	11	6
2	NaH/TBAI	CH ₃ CN	22	6
3	LiHMDS	THF	-	-
4	NaHMDS	THF	11	70
5	KHMDS	THF	16	73
6	BEMP	CH ₃ CN	54	-

[a] Reactions were performed at 0 °C for 2h

With the optimised alkylation conditions in place, a range of propargyl bromides **15a-f** were used to obtain the

corresponding propargylic ethers **2**. These were prepared from commercially available aryl iodides and propargyl alcohol using a two-step process involving Sonogashira coupling¹² followed by conversion of the resulting 3-arylprop-2-ynyl alcohols **14a-f** to their corresponding bromides under Appel conditions (Table 2).

Table 2 : Preparation of 3-arylprop-2-ynyl bromides **15a-f**.

Entry	Ar	Product	Yield, %	Product	Yield, %
1	Ph	14a	nd	15a	83
2	4-Cl-C ₆ H ₄	14b	68	15b	76
3	4-MeO-C ₆ H ₄	14c	84	15c	56
4	4-F-C ₆ H ₄	14d	86	15d	85
5	3-F-C ₆ H ₄	14e	81	15e	70
6	2-F-C ₆ H ₄	14f	55	15f	49

The *O*-alkylation reaction was then performed using the optimized conditions described (Table 3). The crude alkynyl-azido intermediates **2a-k** underwent efficient intramolecular 1,3-dipolar cycloaddition upon heating in toluene for 24 h,¹³

resulting in the novel protected anomeric spironucleoside library **16a-k**.

Table 3 : Alkylation and 1,3-dipolar cycloaddition to access the spirocyclic nucleoside system

Entry	R	Product	Overall yield, %
1	H	16a	51
2	Me	16b	53
3	Et	16c	43
4	2-Naphthyl	16d	59
5	Ph	16e	44
6	4-Cl-C ₆ H ₄	16f	45
7	4-MeO-C ₆ H ₄	16g	43
8	4-F-C ₆ H ₄	16h	43
9	3-F-C ₆ H ₄	16i	39
10	2-F-C ₆ H ₄	16j	45
11	<i>n</i> -Pentyl	16k	36

[a] Overall isolated yield for alkylation and cycloaddition

Debenzoylation of these compounds, using a 7 M solution of ammonia in methanol gave intermediates **17a-k**. X-ray diffraction on a single crystal of **17a** was our first glimpse of the spirocyclic nature of these novel systems (Figure 3). Finally, these acetonide systems were deprotected with acidic resin (Dowex® 50W) to give straightforward access to anomeric spironucleosides **18a-k** in satisfactory yield (Table 4).¹⁴

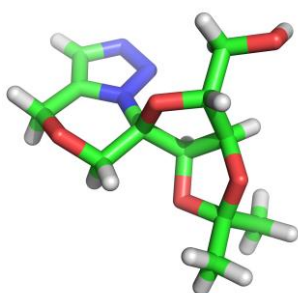


Figure 3 : X-ray crystal structure of **17a** (CCDC 1840501)

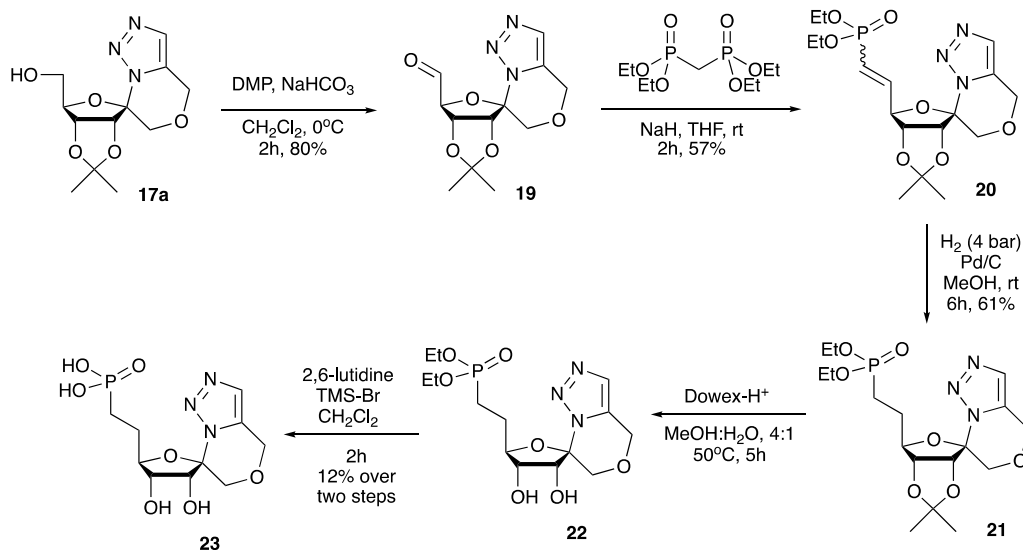
Table 4 : Final deprotection steps to obtain anomeric spirocyclic nucleosides Xa-k

Entry	R	Product	Overall yield, %
1	H	18a	56
2	Me	18b	47
3	Et	18c	51
4	2-Naphthyl	18d	50
5	Ph	18e	67
6	4-Cl-C ₆ H ₄	18f	63
7	4-MeO-C ₆ H ₄	18g	52
8	4-F-C ₆ H ₄	18h	80
9	3-F-C ₆ H ₄	18i	74
10	2-F-C ₆ H ₄	18j	73
11	<i>n</i> -Pentyl	18k	69

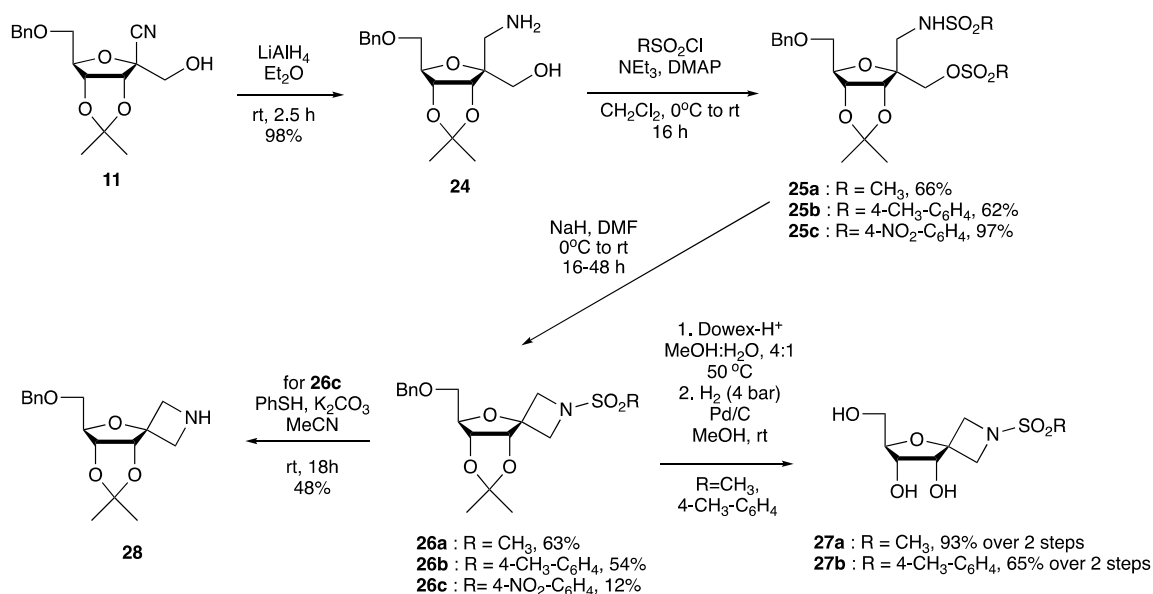
[a] Overall isolated yield for benzoate and acetonide deprotection

2.2 Spiro-[1,2,3]-triazolooxazine Nucleoside Phosphonates

As has been mentioned, the active form of ribavirin is the 5'-phosphate, and as such nucleoside analogues containing the phosphonate moiety as a bioisostere of this have achieved reasonable success.¹⁵ As such we sought to also make the phosphonate **22** as a part of our library (Scheme 2). This was achieved through Dess-Martin oxidation of the 5'-OH in **17a** to the corresponding aldehyde **19** in 80% yield, followed by Horner-Wadsworth-Emmons reaction using tetraethyl methylenediphosphonate to give the corresponding vinyl phosphonate **20** in a 5:2 E/Z ratio. High pressure (4 bar) reduction in methanol gave the corresponding alkyl phosphonate **21** in 61% yield. This underwent deprotection, first of the acetonide using Dowex resin as described previously, followed by deprotection of the phosphonate ester to the corresponding phosphonic acid **23** using trimethylsilyl bromide and 2,6-lutidine in dichloromethane in a 12% overall yield for the two final steps.



Scheme 2 : Synthesis of phosphonate 23



Scheme 3 : Synthesis of azetidinic systems.

2.3 Spirocyclic Azetidines

Another class of spirocyclic nucleoside we were interested in was based on the azetidinic system as described previously by Fuentes and co-workers.¹⁶ In this work, they took the *N*-,*O*-methyl sulfonate **25a** and subjected it to sodium hydride in DMF, whereupon intramolecular cyclisation of the sulfonamide anion onto the *O*-mesylate resulting in the azetidinic system **26a**. We conducted the same reaction for tosyl and nosyl compounds **25b** and **25c**. Subsequently, for the mesyl, and tosyl systems (**26a** and **26b** respectively), we achieved deprotection of the acetonide in the usual way, followed by removal of the benzyl protecting group at high pressure to give spirocyclic

azetidines **27a** and **27b**. The configuration of the tosyl derivative **27b** was determined by X-ray crystallography (Figure 4). The nosyl derivative **26c** was synthesized due to the ease with which it can be removed from the nitrogen atom on which it resides compared to the mesyl and tosyl compounds to expose the secondary amine. However, we were unable to deprotect this compound fully to the corresponding triol but did managed to convert it to the secondary amine intermediate **28**. This possibly represents a useful scaffold to generate a library with structurally diverse spironucleosides.

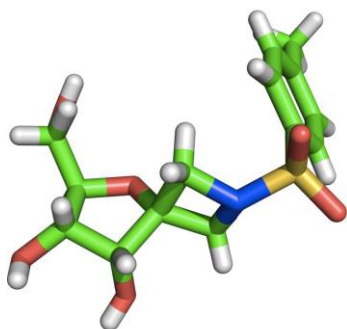


Figure 4 : X-ray crystal structure of novel tosyl azetidinic system **27b**. (CCDC 1840502)

Biological Evaluation

Coronaviruses are an important family of human and veterinary pathogens that can cause enteric and respiratory infections, including severe acute respiratory syndrome coronavirus (SARS) and middle east respiratory syndrome coronavirus (MERS), which are amongst the most lethal viral infections currently known. Infection with the model coronavirus Murine hepatitis virus (MHV) can also lead to gastroenteritis, nephritis, hepatitis, encephalitis, and progressive demyelinating disease, depending on the animal model, virus strain and inoculation route used.¹⁷ Coronaviruses are considered the largest and most complex RNA viruses known, encoding an unusually wide array of proteins that interact with or modify viral RNA.¹⁸ Since coronaviruses are enveloped viruses with a positive-sense RNA genome, they are predicted to be sensitive to RNA-like drugs,¹⁹ and some nucleosides, such as ribavirin **1**, have anti-coronaviral activity.

As a result, Mouse Hepatitis Virus (MHV) has been chosen as a proving ground for the novel nucleoside analogues described in this study for antiviral activity. In order to test for antiviral effects, MHV was grown on mouse 17Cl-1 cells that had been pre-treated with the experimental compounds at a concentration of 1 mM 3 h before inoculation to allow time for drug uptake and potential phosphorylation, inoculated with 10 infectious units of virus per cell for 1 h to ensure as many cells as possible were infected, rinsed with saline to remove any virus that had not entered a cell yet, and incubated again with the same amount of experimental compound for 14 h. The amount of MHV released from infected cells usually peaks at about 14 h after infection (Figure 5a). The amount of virus released from infected cells was then measured by plaque assay. Two of the treatments, **18b** and **18f** reduced the amount of MHV that was released by about tenfold (Figure 5b). Unfortunately, no significant activity was seen for compound **27b** or the phosphonate analogue, compound **22**.

MHV infection in 17Cl-1 cells normally results in formation of large multinucleate syncytia starting about 6 h after infection, followed by detachment of cells from the culture flask and widespread cell death by 14 h after infection.

Compounds were tested for side effects on cell growth (Figure 6a) and then for the ability to protect cells from overt signs of infection (Figure 6b). Selected compounds were tested for side

effects on cell viability and growth over three days of treatment by MTT assay. The most effective experimental compound **18f** did not show any significant toxicity at concentrations of 1 mM and below (Figure 6c). The concentration that produced a 50% reduction in cell viability in these assays was greater than 1 mM for each of the experimental compounds tested, demonstrating that the compounds are relatively non-toxic.

Compound **18f** was then screened for the ability to protect cells from MHV-induced cytopathology, including cell fusion and detachment from the culture flask. The 17Cl-1 cells were pre-treated with **18f** 3 h before infection, rinsed after 24h to remove any dead or detached cells, and surviving adherent cells were photographed 24 h after infection. Treatment with 1 mM compound **18f** resulted in a dose-dependent reduction in both syncytium formation and detachment of infected cells (Figure 6d and 6e).

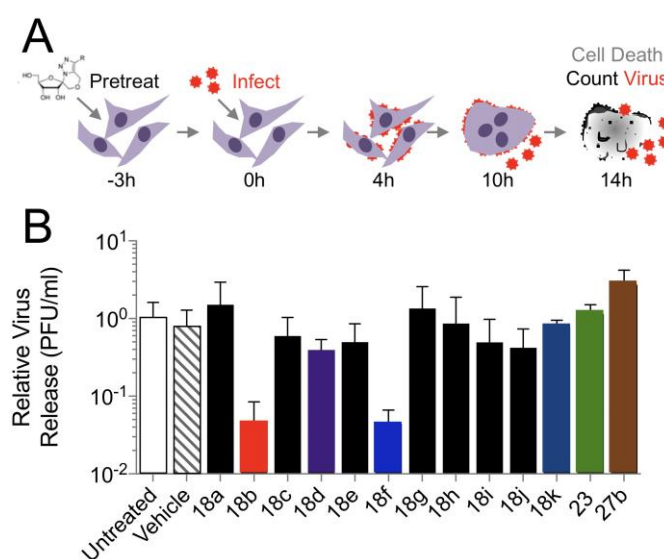


Figure 5. Effects of spirocyclic nucleosides on release of infectious virus. (A) Experimental procedure used to test antiviral efficacy. Mouse 17Cl-1 cells were pre-treated with compounds 3h before inoculation with the virus MHV. After 14h virus growth was measured by plaque assay. (B) Effects of 1 mM treatment on virus release, normalized to virus release from infected untreated cells.

From these data it was concluded that **18f** exerted a limited protective effect on treated cells at concentrations of 250 μ M, and appeared to completely protect treated cells from overt cytopathic effects of virus infection at 2 mM. This also demonstrated that the apparent antiviral activity of **18f** was not simply an artefact of cytotoxicity. More detailed dose-response experiments were performed for four of the experimental compounds in order to better gauge their antiviral potential. The two treatments that were previously identified as most effective, compound **18b** and **18f**, strongly reduced virus growth at 1 mM and 2 mM concentrations, but did not significantly inhibit virus growth at 0.1 mM or lower concentrations (Figure 7) similar to the dose-effectiveness profile of the antiviral nucleoside ribavirin (Fig. 8). Indeed, the low activity of ribavirin against MHV has been well documented.²⁰⁻

²² Two groups using different cell culture methods demonstrated an approximately ten-fold reduction of MHV growth in the presence of 41 micromolar ribavirin,²² and a greater than ten-fold reduction in MHV growth in the presence of a 40 micromolar conjugate of human hemoglobin and ribavirin bound to haptoglobin.²⁰ However, ribavirin treatment has also been shown to reduce the severity of MHV-induced disease in mice and alter the cytokine profile in infected mice.²⁰⁻²² In the investigation of our spirocyclic systems, pre-treatment with 2 mM of **18f** produced the strongest antiviral effects, resulting in approximately one million-fold reduction of MHV growth. Unfortunately, no significant activity was seen for compounds **23** or **27b** at any of the concentrations tested.

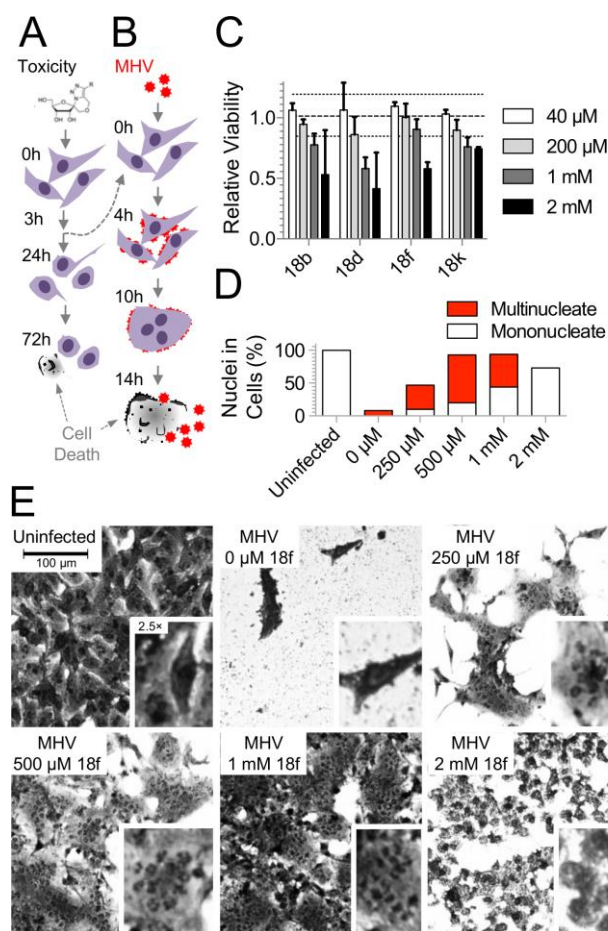


Figure 6. Effects of spirocyclic nucleoside treatment on cells. The experimental procedures used to test for effects on cell viability (A) and the appearance of virus-induced cytopathic effects in mouse 17Cl-1 cells (B) are shown. The effects of experimental compounds on cell viability were assessed by MTT assay 24 hours after treatment (C). Cytopathic effects due to MHV infection were assessed by counting visible nuclei in cells and syncytia after infection in the presence or absence of experimental compounds (D). Representative examples of cells from each treatment group are shown (E) to illustrate the appearance of typical MHV cytopathic effects including formation of multinucleate syncytia (most apparent in 2.5× magnified insets from infected 250 μ M, 500 μ M and 1 mM treatment groups) and loss of cells due to cell destruction (apparent in the infected 0 μ M and 150 μ M treatment groups).

A further experiment was performed in order to learn more about the mechanism of **18f** antiviral activity by evolving drug resistance. MHV was serially passaged eight times on 17Cl-1 cells, which had been pre-treated with 1 mM **18f**, a concentration that reproducibly reduced viral growth by about 90%. Previous work on antiviral compounds suggested that these conditions were appropriate for the selection of drug-resistant coronavirus within about five passages.²³ MHV growth in the presence of **18f** was consistently reduced by about 90% compared to the virus produced in untreated control cells, and did not develop resistance (data not shown). These results suggest that the mechanism of action of **18f** is unclear, and that effects of **18f** on the cell cannot be ruled out as a potential explanation of the antiviral effects.

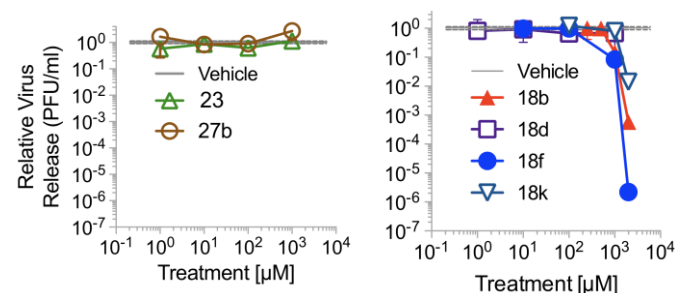


Figure 7. Dose-dependent inhibition of virus growth. The experimental protocol was performed as described in Fig. 6a.

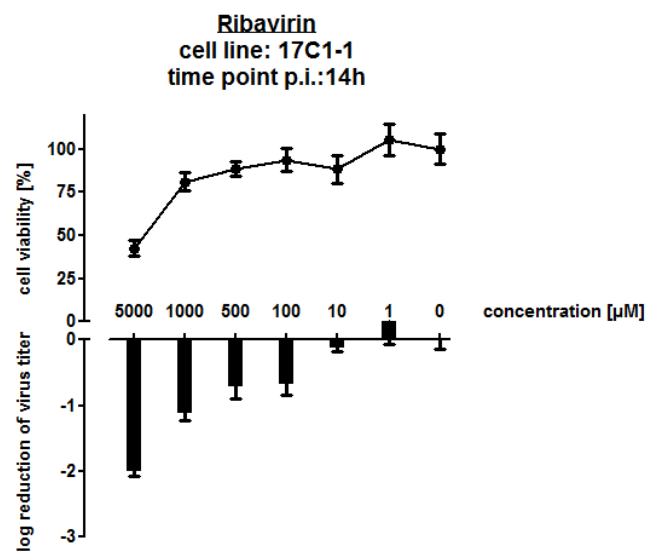


Figure 8. Ribavirin has the similarly low mM cytotoxicity as for our compounds and reduced virus titre in a dose-dependent manner.

Conclusions

In conclusion, we have synthesized an array of spirocyclic ribonucleosides from a common precursor, the protected psicose derivative **6**. Both triazolic and azetidinic systems were accessed, as well as phosphate derivatives. Some of these agents showed

promising activity towards MHV (Mouse Hepatitis Virus), with the most promising being the triazolic system **18f**.

Experimental

Materials and methods

All moisture-sensitive reactions were carried out under an atmosphere of nitrogen. All solvents were analytical grade purity, dried over standard drying agents and stored over 3 Å molecular sieves. All commercially available chemicals were purchased from Sigma Aldrich and used as supplied unless otherwise stated. Reactions were monitored by thin layer chromatography (TLC), which was performed on Merck aluminium backed plates coated with 0.2 mm silica gel 60 F254. The spots were visualised using UV light (254 nm) and then by charring with 10% sulfuric acid in methanol. Column chromatography was carried out using silica gel 60 Å (35–70 µm). ¹H-NMR spectra were recorded in suitable deuterated solvents (CDCl₃, CD₃OD) using a Bruker DPX 400 (400 MHz) or a Bruker Avance III 400 (400 MHz) or a Bruker Avance II+ 500 (500 MHz) spectrometer. In all cases, tetramethylsilane (TMS) was used as internal standard for calibrating chemical shifts (δ), which were quoted in parts per million. Abbreviations were used for the following multiplicities: s, singlet; d, doublet; dd, doublet of doublets; ddd, double double doublet; dt, doublet of triplets; t, triplet; td, triplet of doublets; tt, triplet of triplets; q, quartet; m, multiplet and the coupling constants J were quoted in Hz. ¹³C-NMR spectra were recorded at 100 MHz on a DPX 400 or Avance III 400 or 125 MHz on a Avance II+ 500 in suitable deuterated solvents (CDCl₃, CD₃OD). Assignments were confirmed by homonuclear 2D COSY and heteronuclear 2D correlated experiments (¹H, ¹³CHSQC, ¹H, ¹³C-HMBC). Infrared spectra were recorded on a Perkin-Elmer FT-IR spectrometer as a thin film. The absorptions are quoted in wavenumbers (cm⁻¹). Mass spectrometry data was recorded on a Thermo Scientific LTQ Orbitrap XL using electrospray ionisation (ESI) conditions. Optical rotations were recorded with a Perkin-Elmer 341 polarimeter using a sodium lamp (D line, 589 nm) and mercury lamp (yellow line, 578 nm) as the source of polarized light. They were measured at 20 ± 2 °C in the stated solvent and are quoted in units of 10⁻¹ deg cm² g⁻¹. Solution concentrations (c) are given in the units of 10⁻² g cm⁻³. Melting points are uncorrected and were determined on a Stuart SMP3 melting point apparatus. HPLC analysis was determined on an Agilent Technologies 1200 Series HPLC, using a ratio of HPLC grade hexanes and propan-2-ol as the eluent, using either a Chiralpak AD-H column (0.46 cm Ø X 25 cm) or a Chiralcel OD column (0.46 cm Ø X 25 cm), and detection by UV at 210 nm or 254 nm.

Synthetic Procedures

1,2:3,4-di-O-isopropylidene-β-D-psicofuranose **6**¹⁰

1,2:3,4-di-O-isopropylidene-β-D-psicofuranose **5** (5.0 g, 19.2 mmol) was dissolved in acetone (50 mL). A15 amberlyst resin (250 mg) was added in one portion and the resulting suspension was stirred vigorously for 13 h, then the resin was filtered off, basified with triethylamine and washed with acetone. The filtrate was evaporated under reduced pressure to afford the crude residue as orange oil, which is pure enough to be used immediately for the next step. Purification of the crude product by column chromatography (silica

gel, hexane/ethyl acetate 85/15) gave the pure protected β-D-psicofuranose **6** (4.4 g, 88% yield) as white solid. Data for **6**: White solid, mp = 56–57 °C. [α]_D²⁰ = -92.1 (c = 0.01, CHCl₃). ¹H-NMR (400 MHz, CDCl₃): δ 1.33 (3H, s, CH₃), 1.41 (3H, s, CH₃), 1.45 (3H, s, CH₃), 1.53 (3H, s, CH₃), 3.18 (1H, dd, J = 10.4, 2.8, OH), 3.65 (1H, td, J = 12.4, 3.6, H-6_a), 3.77 (1H, dt, J = 12.4, 2.4, H-6_b), 4.07 (1H, d, J = 10.0, H-1_a), 4.30 (1H, t, J = 2.8, H-5), 4.34 (1H, d, J = 9.8, H-1_b), 4.65 (1H, d, J = 6.0, H-3), 4.92 (1H, dd, J = 6.0, 1.2, H-4). ¹³C-NMR (100 MHz, CDCl₃): 24.8 (CH₃), 26.2 (CH₃), 26.3 (CH₃), 26.5 (CH₃), 64.0 (C-6), 69.9 (C-1), 81.7 (C-4), 85.8 (C-3), 86.8 (C-5), 111.7 (C-2), 112.3 (C(CH₃)₂), 113.4 (C(CH₃)₂). IR (CHCl₃, cm⁻¹): 3480 (br), 2988 (w), 1372 (m), 1209 (m), 1062 (s), 1029 (s), 851 (s).

1,2:3,4-di-O-isopropylidene-6-O-benzoyl-β-D-psicofuranose **7**¹⁰

To a stirring solution of 1,2:3,4-di-O-isopropylidene-β-D-psicofuranose **6** (5.0 g, 19.2 mmol), triethylamine (13 mL, 96.0 mmol) and dimethylaminopyridine (230 mg, 1.92 mmol) in dichloromethane (60 mL) was added benzoyl chloride (2.45 mL, 21.1 mmol) dropwise at 0 °C. The resulting light yellow solution was allowed to warm to room temperature and stirred for 14 h. The mixture was partitioned between saturated aq. NaHCO₃ and dichloromethane. The combined organic layers were washed with brine, dried over MgSO₄, filtered and concentrated to dryness under reduced pressure. Purification of the crude product by column chromatography (silica gel, hexane/ethyl acetate 9/1) gave the title compound **7** (5.6 g, 80% yield) as a white solid. Data for **7**: White solid, mp = 72–73 °C. [α]_D²⁰ = -64.4 (c = 0.01, CHCl₃). ¹H-NMR (400 MHz, CDCl₃): δ 1.34 (3H, s, CH₃), 1.35 (3H, s, CH₃), 1.43 (3H, s, CH₃), 1.47 (3H, s, CH₃), 4.08 (1H, d, J = 9.6, H-1_a), 4.31 (1H, d, J = 9.6, H-1_b), 4.36–4.48 (3H, m, H-3, H-4 and H-5), 4.68 (1H, d, J = 5.6, H-6_a), 4.83 (1H, d, J = 6.0, H-6_b), 7.44 (2H, t, J = 8.0, 2×H_m), 7.57 (1H, tt, J = 7.6, 1.2, H_p), 8.08 (2H, dd, J = 8.4, 1.2, 2×H_o). ¹³C-NMR (100 MHz, CDCl₃): 25.1 (CH₃), 26.2 (CH₃), 26.3 (CH₃), 26.4 (CH₃), 64.8 (C-1), 66.1 (C-6), 82.2 (C-4), 83.0 (C-3), 85.2 (C-5), 111.7 (C-2), 112.8 (C(CH₃)₂), 113.7 (C(CH₃)₂), 128.2 (C_m), 129.7 (C_{ipso}), 129.8 (C_o), 133.1 (C_p), 166.1 (COPh). IR (CHCl₃, cm⁻¹): 2989 (w), 1720 (s), 1373 (m), 1268 (s), 1065 (s), 1024 (s), 854 (s), 709 (s).

1,2:3,4-di-O-isopropylidene-6-O-benzyl-β-D-psicofuranose **8**¹¹

Sodium hydride (60 % dispersion in mineral oil, 5.2 g, 0.13 mol) was placed in a 1L 3 neck round bottom flask equipped with a thermometer and pressure equalising dropping funnel and cooled to 0 °C. Anhydrous DMF (50 mL) was slowly added under inert atmosphere (N₂), ensuring that the internal temperature remained less than 10 °C. A solution of protected D-psicofuranose **6** (28.66 g, 0.11 mol) in anhydrous DMF (200 mL) was then added dropwise over 30 min – again with control of the exotherm and stirred for a further 30 min at 0 °C. A solution of benzyl bromide (19.4 mL, 0.16 mol) in anhydrous DMF (100 mL) was then added dropwise at 0 °C and the resulting solution allowed to warm to room temperature. After this had been achieved, the mixture was stirred for a further 4 h. It was then treated with methanol, diluted with water and extracted with diethylether. The combined organic layers were washed with brine, dried over MgSO₄, filtered and concentrated to dryness under reduced pressure to afford the crude residue as orange oil. Purification of the crude product by column chromatography (silica gel, isohexane/ethyl acetate 9/1) gave the title compound **8** (32.26 g, 84% yield) as colourless syrup. Data for **8**: pale yellow syrup. [α]_D²⁰ = -65.6 (c = 0.01, CHCl₃). ¹H-NMR (400 MHz, CDCl₃): δ 1.29 (3H,

s, CH₃), 1.35 (3H, s, CH₃), 1.41 (3H, s, 2×CH₃), 1.48-1.59 (2H, m, 2×H-6), 4.03 (1H, d, *J* = 9.6, H-1_a), 4.26-4.31 (1H, m, H-5), 4.28 (1H, d, *J* = 9.6, H-1_b), 4.52 (2H, AB q, *J* = 12.4, CH₂Ph), 4.36-4.57 (1H, d, *J* = 5.8, H-3), 4.72 (1H, d, *J* = 5.8, H-4), 7.24-7.32 (5H, m, 5×H_{arom}). ¹³C-NMR (100 MHz, CDCl₃): 25.2 (CH₃), 26.3 (CH₃), 26.4 (CH₃), 26.5 (CH₃), 69.8 (C-1), 70.9 (C-6), 73.3 (C-1'), 82.6 (C-4), 83.8 (C-5), 85.2 (C-3), 111.4 (C-2), 112.5 (C(CH₃)₂), 113.6 (C(CH₃)₂), 127.6 (C_m), 129.6 (C_{ipso}), 129.3 (C_o), 138.2 (C_p). IR (CHCl₃, cm⁻¹): 2941 (w), 1450 (s), 1370 (s).

1-O-Trimethylsilyl-2-azido-2-deoxy-3,4-O-isopropylidene-6-O-benzoyl-β-D-psicofuranose 9¹⁴

To a solution of spiroketal **7** (1.0 g, 2.74 mmol) and freshly distilled acetonitrile (30 mL) was added azidotrimethylsilane (750 μL, 5.48 mmol) at 0 °C under a nitrogen atmosphere in the presence of activated 4Å molecular sieves. The solution was stirred for 5 min and trimethylsilyltriflate (146 μL, 0.82 mmol) added dropwise, and the stirring was continued at 0 °C for a further 5 min. The mixture was neutralized with triethylamine (228 μL, 1.64 mmol), diluted with ethyl acetate and warmed to room temperature. The resulting solution was partitioned between saturated aq. NaHCO₃ and ethyl acetate. The organic layers were washed with brine, dried over MgSO₄, filtered and concentrated to dryness under reduced pressure. Purification of the crude product by column chromatography (silica gel, hexane/ ethyl acetate 95/5) gave the pure **9** (1.03 g, 89% yield) as colourless syrup. Data for **9**: [α]_D²⁰ = -89.6 (c = 0.01, CHCl₃). ¹H NMR (400 MHz, CDCl₃): δ 0.01 (9H, s, Si(CH₃)₃), 1.13 (3H, s, CH₃), 1.47 (3H, s, CH₃), 3.81 (1H, d, *J* = 11.6, H-1_a), 3.84 (1H, d, *J* = 11.2, H-1_b), 4.24-4.28 (2H, m, H-4, H-6_a), 4.33-4.37 (1H, m, H-6_b), 4.42 (1H, td, *J* = 6.4, 1.6, H-5), 4.67 (1H, dd, *J* = 2.0, 6.0, H-3), 7.25 (2H, dd, *J* = 7.6, 7.2, 2×H_m), 7.37 (1H, tt, *J* = 7.6, 1.2, H_p), 7.91 (2H, d, *J* = 7.2, 2×H_o). ¹³C NMR (100 MHz, CDCl₃): 0.0 (Si(CH₃)₃), 25.7 (CH₃), 27.1 (CH₃), 65.0 (C-6), 65.9 (C-1), 83.1 (C-3), 85.3 (C-5), 85.9 (C-4), 101.4 (C-2), 114.1 (C(CH₃)₂), 129.0 (C_m), 130.3 (C_{ipso}), 130.4 (C_o), 133.8 (C_p), 166.7 (COPh). IR (CHCl₃, cm⁻¹): 2956 (w), 2114 (m, N₃), 1723 (s), 1247 (s), 1108 (m, Si-O), 839 (s), 709 (s). HRMS required for C₁₉H₂₇N₃O₆SiNa⁺ is 444.1561, found 444.1561.

2-Azido-2-deoxy-3,4-O-isopropylidene-6-O-benzoyl-β-D-psicofuranose 10¹⁴

To a solution of silyl ether derivative **9** (1.10 g, 2.61 mmol) in acetone (8 mL) were added methanol (10 mL) and glacial acetic acid (553 μL). The solution was stirred for 8 h at room temperature. Then, the reaction mixture was neutralized by triethylamine concentrated under reduced pressure. The resulting residue was partitioned between saturated aq. NaHCO₃ and ethyl acetate. The organic layers were washed with brine, dried over MgSO₄, filtered and concentrated to dryness under reduced pressure. Purification of the crude product by column chromatography (silica gel, hexane/ ethyl acetate 8/2) gave the pure alcohol **10** (893 mg, 98% yield) as colourless syrup. Data for **10**: [α]_D²⁰ = -97.2 (c = 0.01, CHCl₃). ¹H-NMR (400 MHz, CDCl₃): δ 1.32 (3H, s, CH₃), 1.51 (3H, s, CH₃), 3.08 (1H, t, *J* = 6.4, OH), 4.00 (2H, d, *J* = 6.0, H-1_{a,b}), 4.42-4.52 (1H, m, H-6_a), 4.53-4.56 (2H, m, H-3 and H-6_b), 4.63 (1H, td, *J* = 6.0, 1.2, H-5), 4.87 (1H, dd, *J* = 6.0, 1.6, H-4), 7.43 (2H, t, *J* = 7.6, 2×H_m), 7.56 (1H, tt, *J* = 7.6, 1.2, H_p), 8.08 (2H, d, *J* = 7.2, 2×H_o). ¹³C-NMR (100 MHz, CDCl₃): 24.8 (CH₃), 26.1 (CH₃), 64.1 (C-1), 64.3 (C-6), 82.5 (C-4), 84.6 (C-5), 85.4 (C-3), 101.4 (C-2), 113.7 (C(CH₃)₂), 128.5 (C_m), 129.6 (C_{ipso}), 129.7 (C_o), 133.3 (C_p), 166.2 (COPh). IR (CHCl₃, cm⁻¹): 3489 (br), 2956 (w), 2114 (m, N₃), 1720 (s), 1270 (s), 709 (s). HRMS required for C₁₆H₁₉N₃O₆Na⁺ is 372.1166, found 372.1166.

6-O-benzoyl-3,4-O-isopropylidene-β-D-psicofuranosyl cyanide 11¹¹

Spiroketal **8** (38.0 g, 0.11 mol) was placed in a 1L 3 neck round bottom flask equipped with a thermometer and pressure equalising dropping funnel and then cooled to -20 °C under an inert atmosphere of nitrogen. Trimethylsilyl cyanide (40.7 mL, 0.32 mol) was then added dropwise, followed by trimethylsilyl trifluoromethanesulfonate (22.9 mL, 0.16 mol). The reaction mixture was then stirred for 2 h at the same temperature (-20 °C). After this time, it was quenched with saturated sodium bicarbonate solution. The mixture was partitioned between saturated aq. NaHCO₃ and dichloromethane and the aqueous layer treated with sodium hypochlorite. The combined organic layers were washed with brine, dried over MgSO₄, filtered and concentrated to dryness under reduced pressure. Purification of the crude product by column chromatography (silica gel, isohexane/ ethyl acetate 75/25) gave the title compound **11** (20.4 g, 58% yield) as colourless syrup. Data for **11**: Oil. [α]_D²⁰ = -29.0 (c = 0.01, CHCl₃). ¹H-NMR (400 MHz, CDCl₃): δ 1.34 (3H, s, CH₃), 1.52 (3H, s, CH₃), 2.61 (1H, br, OH), 3.54-3.65 (2H, m, 2×H-6), 3.89 (2H, s, 2×H-1), 4.42 (1H, m, H-5), 4.50 (1H, d, *J* = 12.1, H-7_a), 4.69 (1H, d, *J* = 12.1, H-7_b), 4.90 (1H, d, *J* = 5.9, H-3), 5.09 (1H, d, *J* = 5.8, H-4), 7.30-7.36 (5H, m, 5×H_{arom}). ¹³C-NMR (100 MHz, CDCl₃): 24.5 (CH₃), 25.7 (CH₃), 64.9 (C-1), 70.1 (C-6), 73.5 (C-7), 82.9 (C-2), 83.3 (C-3), 84.9 (C-5), 85.2 (C-4), 113.9 (C(CH₃)₂), 120.0 (CN), 127.9 (C_p), 128.1 (C_o), 128.5 (C_m), 137.3 (C_{ipso}). IR (CHCl₃, cm⁻¹): 3298 (br), 2940 (w), 1714 (m), 1453 (m), 1360 (m).

((3aR,4R,6R,6aR)-6-azido-2,2-dimethyl-6-((prop-2-yn-1-yloxy)methyl)tetrahydrofuro[3,4-d][1,3]dioxol-4-yl)methyl benzoate 2a

Azido alcohol **10** (500 mg, 1.43 mmol) was dried by evaporation of freshly distilled acetonitrile and dissolved in the same solvent (8.4 mL). To the resulting solution were added BEMP (497 μL, 1.72 mmol) followed by the suitable propargyl bromide (2.15 mmol) dropwise at 0 °C under a nitrogen atmosphere. The reaction mixture was stirred at the same conditions until TLC indicated completion of the reaction (2-4h). The resulting solution was partitioned between phosphate buffer solution pH 7.00 and ethyl acetate. The organic layers were washed with 10% NaCl aq. solution, dried over MgSO₄, filtered and concentrated to dryness under reduced pressure to afford the crude residue as brown oil which in the majority of cases was used crude in the following cycloaddition step owing to spontaneous reactivity and in an effort to maximise overall yield. The characterisation for the purified intermediates is described below.

Chromatography of the crude residue over silica gel (hexane/ethyl acetate 8/2) gave the pure **2a** (299 mg, 54% yield). Data for **2a**: Colourless oil, [α]_D²⁰ = -86.5 (c = 0.02, CHCl₃). ¹H-NMR (400 MHz, CDCl₃): δ 1.21 (3H, s, CH₃), 1.49 (3H, s, CH₃), 2.42 (1H, t, *J* = 2.4, H-3'), 3.89 (2H, s, H-1_{a,b}), 4.25 (2H, d, *J* = 2.0, H-1' _{a,b}), 4.33-4.49 (3H, m, H-3, H-6_{a,b}), 4.54 (1H, td, *J* = 6.4, 1.6, H-5), 4.80 (1H, dd, *J* = 6.4, 1.6, H-4), 7.39 (2H, t, *J* = 8.0, 2×H_m), 7.51 (1H, t, *J* = 7.2, H_p), 8.02 (2H, d, *J* = 7.6, 2×H_o). ¹³C-NMR (100 MHz, CDCl₃): 25.1 (CH₃), 26.5 (CH₃), 59.1 (C-1'), 64.2 (C-6), 70.4 (C-1), 75.2 (C-3'), 79.3 (C-2'), 82.5 (C-4), 85.0 (C-5), 85.5 (C-3), 100.7 (C-2), 114.0 (C(CH₃)₂), 128.5 (C_m), 129.7 (C_{ipso}), 129.8 (C_o), 133.4 (C_p), 166.3 (COPh). IR (CHCl₃, cm⁻¹): 3292 (w), 2927 (w), 2116 (m, N₃), 1721 (s), 1270 (s), 1270 (s), 1068 (m), 711 (s). HRMS required for C₁₉H₂₂N₃O₆⁺ is 388.1503, found 388.1505.

2-Azido-2-deoxy-3,4-O-isopropylidene- β -D-psicofuranose **12**

To a solution of compound **10** (75 mg, 0.21 mmol) in freshly distilled THF (1.5 mL), a solution of NaHDMS (47 mg, 0.26 mmol) was added dropwise at 0 °C under nitrogen atmosphere. After 5 min, propargyl bromide (36 μ L, 0.32 mmol) was added and the reaction mixture was stirred for 4 h. Afterwards, saturated aq. NH₄Cl was added and the resulting emulsion was extracted with ethyl acetate and washed with brine. The organic layers were dried over MgSO₄, filtered and the solvent evaporated under reduced pressure. Chromatography of the crude residue over silica gel gave azidoalkyne **2a** (hexane/ethyl acetate 8/2) as the minor product (9 mg, 11% yield) and debenzoylated psicofuranose **12** (hexane/ethyl acetate 6/4) as major product (36 mg, 70% yield). Data for **12**: Colourless syrup, ¹H-NMR (400 MHz, CDCl₃): δ 1.27 (3H, s, CH₃), 1.46 (3H, s, CH₃), 2.27 (2H, br, 2 \times OH), 3.65-3.74 (2H, m, H-6_{a,b}), 3.91 (2H, s, H-1_{a,b}), 4.33 (1H, td, J = 6.0, 1.6, H-5), 4.46 (1H, d, J = 6.0, H-3), 4.75 (1H, dd, J = 6.0, 1.6, H-4). ¹³C-NMR (100 MHz, CDCl₃): 23.4 (CH₃), 25.2 (CH₃), 62.4 (C-6), 63.4 (C-1), 81.1 (C-4), 84.7 (C-3), 86.6 (C-5), 100.3 (C-2), 112.6 (C(CH₃)₂).

General Procedure for Sonogashira Coupling

To a stirring suspension of aryl iodide (4.2 mmol), dichlorobis(triphenylphosphine)palladium(II) (30 mg, 0.042 mmol), copper(I) iodide (4 mg, 0.021 mmol) and freshly distilled diethylamine (50 mL) was added propargyl alcohol (4.2 mmol) dropwise under a N₂ atmosphere.

The resulting reaction mixture was stirred for 5 h at room temperature. After this time, diethylamine was removed under reduced pressure and the crude product was partitioned between water and diethyl ether. The combined organic layers were washed with brine, dried (MgSO₄), filtered and concentrated under reduced pressure.

General procedure for O-alkylation and intramolecular 1,3-dipolar cycloaddition¹⁴

Azido alcohol **10** (500 mg, 1.43 mmol) was dried by evaporation of freshly distilled acetonitrile and dissolved in the same solvent (8.4 mL). To the resulting solution BEMP (497 μ L, 1.72 mmol) and the suitable propargyl bromide (2.15 mmol) were added drop-wise at 0 °C under a nitrogen atmosphere. The reaction mixture was stirred under these conditions until TLC indicated completion of the reaction (2-4 h). The resulting solution was partitioned between phosphate buffer solution pH 7 and ethyl acetate. The organic layers were washed with 10% NaCl aq. solution, dried over MgSO₄, filtered, and concentrated under reduced pressure to afford the crude residue as brown oil which in the majority of cases was used as telescoped material in the following cycloaddition step owing to spontaneous reactivity and in an effort to maximise overall yield. Thus, the crude azido alkyne **2a-k** was dissolved in toluene (28.6 mL) and refluxed until TLC analysis showed full conversion to corresponding triazolo-oxazine **16a-k** (16-24 h). The solvent was removed under reduced pressure and the residue was purified on silica gel.

((3aR,4R,6R,6aR)-2,2-dimethyl-3a,6a-dihydro-4'H,6H,6'H-spiro[furo[3,4-d][1,3]dioxole-4,7'-[1,2,3]triazolo[5,1-c][1,4]oxazin]-6-yl)methyl benzoate **16a**

Chromatography of the crude residue over silica gel (hexane/ethyl acetate 6/4) gave the pure triazolo-oxazine **16a** (282 mg, 95% yield). Data for **16a**: Colourless oil, $[\alpha]_D^{20} = -11.87$ ($c = 0.0016$, CHCl₃). ¹H-NMR (400 MHz, CDCl₃): δ 1.37 (3H, s, CH₃), 1.60 (3H, s, CH₃), 4.19 (1H, d, J = 8.0, H-1_a), 4.23 (1H, d, J = 8.2, H-1_b), 4.55-4.69 (3H, m, H-5, H-6_{a,b}), 4.83 (1H, d, J = 15.2, H-1'_a), 5.04 (1H, d, J = 15.2, H-1'_b), 5.16 (1H, d, J = 6.0, H-3), 5.30-5.31 (1H, m, H-4), 7.43 (2H, td, J = 7.8, 1.6, 2 \times H_m), 7.52 (1H, s, H-3'), 7.55 (1H, tt, J = 7.3, 1.2, H_p), 8.06 (2H, dd, J = 8.0, 1.6, 2 \times H_o). ¹³C-NMR (100 MHz, CDCl₃): 25.3 (CH₃), 26.8 (CH₃), 62.5 (C-1'), 64.5 (C-6), 69.1 (C-1), 83.2 (C-4), 85.2 (C-3), 86.3 (C-5), 93.1 (C-2), 114.4 (C(CH₃)₂), 128.1 (C-3'), 128.3 (C_m), 129.7 (C_{ipso}), 129.8 (C_o), 131.4 (C-2'), 133.1 (C_p), 166.1 (COPh). IR (CHCl₃, cm⁻¹): 2923 (w), 1721 (s), 1269 (s), 1094 (s), 1068 (m), 713 (s). HRMS required for C₁₉H₂₂N₃O₆⁺ is 388.1503, found 388.1506.

((3aR,4R,6R,6aR)-2,2,3'-trimethyl-3a,6a-dihydro-4'H,6H,6'H-spiro[furo[3,4-d][1,3]dioxole-4,7'-[1,2,3]triazolo[5,1-c][1,4]oxazin]-6-yl)methyl benzoate **16b**

Chromatography of the crude residue over silica gel (hexane/ethyl acetate 6/4) gave the pure triazolo-oxazine **16b** (304 mg, 96% yield). Data for **16b**: Colourless oil, $[\alpha]_D^{20} = -24.82$ ($c = 0.01$, CHCl₃). ¹H-NMR (400 MHz, CDCl₃): δ 1.38 (3H, s, CH₃), 1.59 (3H, s, CH₃), 2.27 (3H, s, 3 \times H-4'), 4.15 (1H, d, J = 12.8, H-1_a), 4.22 (1H, d, J = 12.4, H-1_b), 4.53-4.67 (3H, m, H-5, H-6_{a,b}), 4.73 (1H, d, J = 14.8, H-1'_a), 4.95 (1H, d, J = 14.8, H-1'_b), 5.15 (1H, d, J = 6.0, H-3), 5.28 (1H, dd, J = 6.0, 2.8, H-4), 7.43 (2H, t, J = 7.2, 2 \times H_m), 7.55 (1H, t, J = 7.6, H_p), 8.06 (2H, d, J = 7.8, 2 \times H_o). ¹³C-NMR (100 MHz, CDCl₃): 10.0 (C-4'), 25.3 (CH₃), 26.8 (CH₃), 62.3 (C-1'), 64.6 (C-6), 68.9 (C-1), 83.2 (C-4), 85.1 (C-5), 86.1 (C-6), 93.0 (C-2), 114.4 (C(CH₃)₂), 127.8 (C-3'), 128.7 (C_m), 129.8 (C_{ipso}), 129.9 (C_o), 133.0 (C_p), 137.0 (C-2'), 166.1 (COPh). IR (CHCl₃, cm⁻¹): 2989 (w), 1719 (s), 1269 (s), 1096 (s), 1068 (m), 709 (s). HRMS required for C₂₀H₂₄N₃O₆⁺ is 402.1660, found 402.1658.

((3aR,4R,6R,6aR)-3'-ethyl-2,2-dimethyl-3a,6a-dihydro-4'H,6H,6'H-spiro[furo[3,4-d][1,3]dioxole-4,7'-[1,2,3]triazolo[5,1-c][1,4]oxazin]-6-yl)methyl benzoate **16c**

Chromatography of the crude residue over silica gel (hexane/ethyl acetate 6/4) gave the pure triazolo-oxazine **79c** (255 mg, 82% yield). Data for **79c**: Colourless oil, $[\alpha]_D^{20} = -27.26$ ($c = 0.015$, CHCl₃). ¹H-NMR (400 MHz, CDCl₃): δ 1.26 (3H, t, J = 7.6, 3 \times H-5'), 1.38 (3H, s, CH₃), 1.59 (3H, s, CH₃), 2.67 (2H, q, J = 7.6, 2 \times H-4'), 4.17 (1H, d, J = 12.8, H-1_a), 4.22 (1H, d, J = 12.8, H-1_b), 4.54-4.67 (3H, m, H-5, H-6_{a,b}), 4.76 (1H, d, J = 14.8, H-1'_a), 4.97 (1H, d, J = 14.8, H-1'_b), 5.15 (1H, d, J = 6.0, H-3), 5.29 (1H, dd, J = 5.6, 2.8, H-4), 7.43 (2H, t, J = 7.6, 2 \times H_m), 7.55 (1H, t, J = 7.2, H_p), 8.05 (2H, d, J = 7.8, 2 \times H_o). ¹³C-NMR (100 MHz, CDCl₃): 13.2 (C-5'), 18.5 (C-4'), 25.3 (CH₃), 26.8 (CH₃), 62.4 (C-1'), 64.6 (C-6), 68.9 (C-1), 83.3 (C-4), 85.1 (C-5), 86.1 (C-6), 93.1 (C-2), 114.3 (C(CH₃)₂), 127.3 (C-3'), 128.3 (C_m), 129.8 (C_{ipso}), 129.8 (C_o), 133.1 (C_p), 142.8 (C-2'), 166.1 (COPh). IR (CHCl₃, cm⁻¹): 2978 (w), 1720 (s), 1271 (s), 1098 (s), 1069 (m), 712 (s). HRMS required for C₂₁H₂₆N₃O₆⁺ is 416.1803, found 416.1809.

((3aR,4R,6R,6aR)-2,2-dimethyl-3'-(naphthalen-2-yl)-3a,6a-dihydro-4'H,6H,6'H-spiro[furo[3,4-d][1,3]dioxole-4,7'-[1,2,3]triazolo[5,1-c][1,4]oxazin]-6-yl)methyl benzoate **16d**

Chromatography of the crude residue over silica gel (hexane/ethyl acetate 8/2) gave the pure triazolooxazine **16d** (433 mg, 94% yield). Data for **16d**: Colourless oil, $[\alpha]_D^{20} = -36.46$ ($c = 0.015$, CHCl_3). $^1\text{H-NMR}$ (400 MHz, CDCl_3): 1.42 (3H, s, CH_3), 1.63 (3H, s, CH_3), 4.29 (1H, d, $J = 12.8$, H-1_a), 4.34 (1H, d, $J = 12.4$, H-1_b), 4.70-4.77 (3H, m, H-5, H-6_{a,b}), 4.81 (1H, d, $J = 15.2$, H-1'_a), 4.97 (1H, d, $J = 15.2$, H-1'_b), 5.29 (1H, d, $J = 6.0$, H-3), 5.39 (1H, dd, $J = 5.6$, 2.4, H-4), 7.40-7.46 (3H, m, H-Naph, 2 \times H_m), 7.47-7.55 (4H, m, 3 \times H-Naph, H_p), 7.89-7.91 (2H, m, 2 \times H-Naph), 8.09-8.015 (3H, m, H-Naph, 2 \times H_o). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): 25.4 (CH_3), 26.9 (CH_3), 63.2 (C-1'), 64.6 (C-6), 69.1 (C-1), 83.2 (C-4), 85.3 (C-5), 86.3 (C-6), 93.5 (C-2), 114.5 ($\text{C}(\text{CH}_3)_2$), 125.2, 125.5, 126.3, 126.6 (Naph), 127.4 (C-3'), 128.4 (C_m), 128.5, 129.3 (Naph), 129.7 (C_{ipso}), 129.8 (C_o), 129.9 (Naph), 131.4 (C-2'), 133.1 (C_p), 133.9 (Naph), 141.0 (C_{ipso}-Naph), 166.2 (COPh). IR (CHCl_3 , cm^{-1}): 2990 (w), 1719 (s), 1271 (s), 1097 (s), 1069 (s), 1025 (m), 751 (s), 710 (s). HRMS required for $\text{C}_{29}\text{H}_{28}\text{N}_3\text{O}_6^+$ is 514.1973, found 514.1970.

((3aR,4R,6R,6aR)-3'-(4-methoxyphenyl)-2,2-dimethyl-3a,6a-dihydro-4'H,6H,6'H-spiro[furo[3,4-d][1,3]dioxole-4,7'-[1,2,3]triazolo[5,1-c][1,4]oxazin]-6-yl)methyl benzoate 16e

Chromatography of the crude residue over silica gel (hexane/ethyl acetate 8/2) gave the pure triazolooxazine **16e** (291 mg, 44% yield over two steps) as a white solid. Data for **16e**: Mp = 72-73°C. $[\alpha]_D^{20} = -31.6$ ($c = 0.01$, CHCl_3). $^1\text{H-NMR}$ (400 MHz, CDCl_3): 1.40 (3H, s, CH_3), 1.61 (3H, s, CH_3), 4.25 (1H, d, $J = 12.8$, H-1_a), 4.29 (1H, d, $J = 12.8$, H-1_b), 4.58-4.72 (3H, m, H-5, H-6_{a,b}), 5.01 (1H, d, $J = 15.2$, H-1'_a), 5.21 (1H, d, $J = 15.2$, H-1'_b), 5.21 (1H, d, $J = 6.0$, H-3), 5.33 (1H, dd, $J = 5.8$, 2.8, H-4), 7.35 (1H, t, $J = 7.2$, H-7'), 7.40-7.47 (4H, m, 2 \times H-6', 2 \times H_m), 7.55 (1H, t, $J = 7.2$, H_p), 7.62 (2H, d, $J = 7.6$, 2 \times H-5'), 8.06 (2H, d, $J = 7.2$, 2 \times H_o). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): 25.3 (CH_3), 26.8 (CH_3), 63.4 (C-1'), 64.6 (C-6), 68.8 (C-1), 83.3 (C-4), 85.2 (C-3), 86.3 (C-5), 93.3 (C-2), 114.4 ($\text{C}(\text{CH}_3)_2$), 126.2 (C-5'), 127.2 (C-2'), 128.2 (C-7'), 128.4 (C_m), 129.0 (C-6'), 129.8 (C_{ipso}), 129.9 (C_o), 130.3 (C-4'), 133.1 (C_p), 141.4 (C-3'), 166.2 (COPh). IR (CHCl_3 , cm^{-1}): 2924 (w), 2358 (s), 1719 (s), 1270 (s), 1097 (s), 1069 (s), 1025 (m), 749 (s), 709 (s). HRMS required for $\text{C}_{25}\text{H}_{26}\text{N}_3\text{O}_6^+$ is 464.1816, found 464.1813.

((3aR,4R,6R,6aR)-3'-(4-chlorophenyl)-2,2-dimethyl-3a,6a-dihydro-4'H,6H,6'H-spiro[furo[3,4-d][1,3]dioxole-4,7'-[1,2,3]triazolo[5,1-c][1,4]oxazin]-6-yl)methyl benzoate 16f

Chromatography of the crude residue over silica gel (hexane/ethyl acetate 8/2) gave the pure triazolooxazine **16f** (320 mg, 45% yield over two steps) as white solid. Data for **16f**: Mp = 74-75°C. $[\alpha]_D^{20} = -28.7$ ($c = 0.01$, CHCl_3). $^1\text{H-NMR}$ (400 MHz, CDCl_3): 1.39 (3H, s, CH_3), 1.61 (3H, s, CH_3), 4.25 (1H, d, $J = 12.8$, H-1_a), 4.29 (1H, d, $J = 12.8$, H-1_b), 4.57-4.72 (3H, m, H-5, H-6_{a,b}), 4.99 (1H, d, $J = 15.2$, H-1'_a), 5.19 (1H, d, $J = 15.2$, H-1'_b), 5.21 (1H, d, $J = 6.0$, H-3), 5.32 (1H, dd, $J = 6.0$, 2.8, H-4), 7.41-7.45 (4H, m, 2 \times H-6', 2 \times H_m), (2H, d, $J = 7.2$, 2 \times H-5'), 8.06 (2H, d, $J = 7.2$, 2 \times H_o). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): 25.3 (CH_3), 26.8 (CH_3), 63.3 (C-1'), 64.6 (C-6), 68.8 (C-1), 83.2 (C-4), 85.2 (C-3), 86.3 (C-5), 93.5 (C-2), 114.5 ($\text{C}(\text{CH}_3)_2$), 127.3 (C-5'), 127.9 (C-2'), 128.4 (C_m), 128.9 (C-4'), 129.3 (C-6'), 129.8 (C_{ipso}), 129.9 (C_o), 133.1 (C_p), 134.0 (C-3'), 166.1 (COPh). IR (CHCl_3 , cm^{-1}): 2988 (w), 1718 (s), 1491 (m), 1271 (s), 1090 (s), 1069 (s), 1025 (m), 1001 (s), 752 (s), 711(s). HRMS required for $\text{C}_{25}\text{H}_{25}\text{N}_3\text{O}_6\text{Cl}^+$ is 498.1432, found 498.1426.

((3aR,4R,6R,6aR)-3'-(4-methoxyphenyl)-2,2-dimethyl-3a,6a-dihydro-4'H,6H,6'H-spiro[furo[3,4-d][1,3]dioxole-4,7'-[1,2,3]triazolo[5,1-c][1,4]oxazin]-6-yl)methyl benzoate 16g

Chromatography of the crude residue over silica gel (hexane/ethyl acetate 7/3) gave the pure triazolooxazine **16g** (303 mg, 43% yield over two steps) as white solid. Data for **16g**: Mp = 128-129°C. $[\alpha]_D^{20} = -32.6$ ($c = 0.01$, CHCl_3). $^1\text{H-NMR}$ (400 MHz, CDCl_3): 1.39 (3H, s, CH_3), 1.60 (3H, s, CH_3), 3.84 (3H, s, OCH_3), 4.23 (1H, d, $J = 12.4$, H-1_a), 4.28 (1H, d, $J = 12.8$, H-1_b), 4.58-4.71 (3H, m, H-5, H-6_{a,b}), 4.97 (1H, d, $J = 14.8$, H-1'_a), 5.17 (1H, d, $J = 15.2$, H-1'_b), 5.20 (1H, d, $J = 6.4$, H-3), 5.32 (1H, dd, $J = 5.8$, 2.8, H-4), 6.98 (2H, d, $J = 8.8$, 2 \times H-6'), 7.42 (2H, t, $J = 7.6$, 2 \times H_m), 7.52-7.56 (1H, m, H_p), 7.52 (2H, d, $J = 8.8$, 2 \times H-5'), 8.06 (2H, d, $J = 7.2$, 2 \times H_o). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): 25.3 (CH_3), 26.8 (CH_3), 55.3 (OCH_3), 63.4 (C-1'), 64.7 (C-6), 68.8 (C-1), 83.3 (C-4), 85.2 (C-3), 86.3 (C-5), 93.4 (C-2), 114.4 ($\text{C}(\text{CH}_3)_2$), 114.5 (C-6'), 123.0 (C-4'), 126.8 (C-2'), 127.5 (C-5'), 128.3 (C_m), 129.8 (C_{ipso}), 129.9 (C_o), 133.1 (C_p), 141.2 (C-3'), 160.0 (C-7'), 166.1 (COPh). IR (CHCl_3 , cm^{-1}): 2938 (w), 1720 (s), 1507 (s), 1271 (s), 1248 (s), 1098 (s), 1069 (s), 1025 (m), 753 (s), 711(s). HRMS required for $\text{C}_{26}\text{H}_{28}\text{N}_3\text{O}_7^+$ is 494.1922, found 494.1922.

((3aR,4R,6R,6aR)-3'-(4-fluorophenyl)-2,2-dimethyl-3a,6a-dihydro-4'H,6H,6'H-spiro[furo[3,4-d][1,3]dioxole-4,7'-[1,2,3]triazolo[5,1-c][1,4]oxazin]-6-yl)methyl benzoate 16h

Chromatography of the crude residue over silica gel (hexane/ethyl acetate 8/2) gave the pure triazolooxazine **16h** (296 mg, 43% yield over two steps) as colourless oil. Data for **16h**: $[\alpha]_D^{20} = -32.6$ ($c = 0.01$, CHCl_3). $^1\text{H-NMR}$ (400 MHz, CDCl_3): 1.39 (3H, s, CH_3), 1.61 (3H, s, CH_3), 4.24 (1H, d, $J = 12.4$, H-1_a), 4.29 (1H, d, $J = 12.8$, H-1_b), 4.57-4.72 (3H, m, H-5, H-6_{a,b}), 4.98 (1H, d, $J = 15.2$, H-1'_a), 5.18 (1H, d, $J = 15.2$, H-1'_b), 5.21 (1H, d, $J = 6.0$, H-3), 5.32 (1H, dd, $J = 6.0$, 2.8, H-4), 7.14 (2H, t, $J = 8.8$, 2 \times H-6'), 7.42 (2H, app t, $J = 8.0$, 2 \times H_m), 7.55 (1H, t, $J = 7.2$, H_p), 7.59 (2H, dd, $J = 8.2$, 5.2, 2 \times H-5'), 8.06 (2H, d, $J = 7.2$, 2 \times H_o). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): 25.3 (CH_3), 26.8 (CH_3), 63.3 (C-1'), 64.6 (C-6), 68.8 (C-1), 83.2 (C-4), 85.2 (C-3), 86.3 (C-5), 93.4 (C-2), 114.5 ($\text{C}(\text{CH}_3)_2$), 116.1 (d, $^2J_{\text{CF}} = 22$, C-6'), 126.5 (d, $^4J_{\text{CF}} = 3$, C-4'), 127.5 (C-2'), 127.9 (d, $^3J_{\text{CF}} = 8$, C-5'), 128.4 (C_m), 129.7 (C_{ipso}), 129.8 (C_o), 133.1 (C_p), 140.5 (C-3'), 162.5 (d, $^1J_{\text{CF}} = 246$, C-7'), 166.1 (COPh). IR (CHCl_3 , cm^{-1}): 2933 (w), 1719 (s), 1505 (s), 1272 (s), 1099 (s), 1069 (s), 1026 (m), 759 (s), 711(s). HRMS required for $\text{C}_{25}\text{H}_{25}\text{N}_3\text{O}_6\text{F}^+$ is 482.1722, found 482.1720.

((3aR,4R,6R,6aR)-3'-(3-fluorophenyl)-2,2-dimethyl-3a,6a-dihydro-4'H,6H,6'H-spiro[furo[3,4-d][1,3]dioxole-4,7'-[1,2,3]triazolo[5,1-c][1,4]oxazin]-6-yl)methyl benzoate 16i

Chromatography of the crude residue over silica gel (hexane/ethyl acetate 8/2) gave the pure triazolooxazine **16i** (268 mg, 39% yield over two steps) as colourless oil. Data for **16i**: $[\alpha]_D^{20} = -40.2$ ($c = 0.01$, CHCl_3). $^1\text{H-NMR}$ (400 MHz, CDCl_3): 1.40 (3H, s, CH_3), 1.61 (3H, s, CH_3), 4.24 (1H, d, $J = 12.8$, H-1_a), 4.30 (1H, d, $J = 12.8$, H-1_b), 4.58-4.71 (3H, m, H-5, H-6_{a,b}), 5.00 (1H, d, $J = 15.2$, H-1'_a), 5.21 (1H, dd, $J = 15.2$, H-1'_b), 5.22 (1H, d, $J = 6.0$, H-3), 5.32 (1H, dd, $J = 6.0$, 2.8, H-4), 7.05 (1H, td, $J = 8.4$, 1.6, H-7'), 7.32-7.45 (5H, m, H-5', H-8', H-9', 2 \times H_m), 7.35 (1H, dd, $J = 13.6$, 6.4, H-7'), 7.42 (2H, t, $J = 8.0$, H_m), 7.55 (1H, t, $J = 6.8$, H_p), 8.07 (2H, d, $J = 7.6$, 2 \times H_o). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): 25.3

(CH₃), 26.8 (CH₃), 63.3 (C-1'), 64.6 (C-6), 68.8 (C-1), 83.2 (C-4), 85.2 (C-3), 86.3 (C-5), 93.5 (C-2), 113.1 (d, ²J_{CF} = 23, C-5'), 114.5 (C(CH₃)₂), 115.0 (d, ²J_{CF} = 22, C-7'), 121.7 (d, ⁴J_{CF} = 3, C-9'), 128.2 (C-2'), 128.4 (C_m), 129.7 (C_{ipso}), 129.9 (C_o), 130.6 (d, ³J_{CF} = 8, C-8'), 132.4 (d, ³J_{CF} = 8, C-4'), 133.1 (C_p), 140.3 (d, ⁴J_{CF} = 3, C-3'), 163.2 (d, ¹J_{CF} = 245, C-6'), 166.1 (COPh). IR (CHCl₃, cm⁻¹): 2987 (w), 1718 (s), 1270 (s), 1097 (s), 1070 (s), 1026 (m), 754 (s), 711(s). HRMS required for C₂₅H₂₅N₃O₆F⁺ is 482.1722, found 482.1722.

((3aR,4R,6R,6aR)-3'-(2-fluorophenyl)-2,2-dimethyl-3a,6a-dihydro-4'H,6H,6'H-spiro[furo[3,4-d][1,3]dioxole-4,7'-[1,2,3]triazolo[5,1-c][1,4]oxazin]-6-yl)methyl benzoateSpirocyclic triazolo-oxazine 16j
Chromatography of the crude residue over silica gel (hexane/ethyl acetate 8/2) gave the pure triazolooxazine **16j** (310 mg, 45% yield over two steps) as colourless oil. Data for **16j**: [α]_D²⁰ = -36.5 (c = 0.01, CHCl₃). ¹H-NMR (400 MHz, CDCl₃): 1.39 (3H, s, CH₃), 1.60 (3H, s, CH₃), 4.25 (1H, d, J = 14.0, H-1_a), 4.29 (1H, d, J = 13.6, H-1_b), 4.59-4.74 (3H, m, H-5, H-6_{a,b}), 4.92 (1H, dd, J = 15.8, 2.4, H-1'_a), 5.09 (1H, dd, J = 15.8, 2.4, H-1'_b), 5.20 (1H, d, J = 6.0, H-3), 5.34 (1H, dd, J = 5.6, 2.8, H-4), 7.11 (1H, t, J = 8.4, H-6'), 7.26 (1H, t, J = 8.4, H-8'), 7.35 (1H, dd, J = 13.6, 6.4, H-7'), 7.42 (2H, t, J = 8.0, 2×H_m), 7.55 (1H, t, J = 6.8, H_p), 7.98 (1H, td, J = 7.6, 1.6, H-9'), 8.07 (2H, d, J = 7.2, 2×H_o). ¹³C-NMR (100 MHz, CDCl₃): 25.3 (CH₃), 26.8 (CH₃), 63.8 (d, ⁵J_{CF} = 18, C-1'), 64.7 (C-6), 68.8 (C-1), 83.2 (C-4), 85.2 (C-3), 86.3 (C-5), 93.6 (C-2), 114.4 (C(CH₃)₂), 115.7 (d, ²J_{CF} = 21, C-6'), 118.1 (d, ²J_{CF} = 15, C-4'), 124.8 (d, ⁴J_{CF} = 3, C-8'), 128.3 (C_m), 129.6 (C-2'), 129.7 (C_{ipso}), 129.8 (C_o), 129.9 (d, ⁵J_{CF} = 4, C-9') 130.2 (d, ³J_{CF} = 9, C-7'), 133.1 (C_p), 136.1 (C-3'), 162.5 (d, ¹J_{CF} = 244, C-5'), 166.1 (COPh). IR (CHCl₃, cm⁻¹): 2986 (w), 1720 (s), 1272 (s), 1097 (s), 1101 (s), 1069 (m), 757 (s), 711(s). HRMS required for C₂₅H₂₅N₃O₆F⁺ is 482.1722, found 482.1722.

((3aR,4R,6R,6aR)-2,2-dimethyl-3'-(4-pentylphenyl)-3a,6a-dihydro-4'H,6H,6'H-spiro[furo[3,4-d][1,3]dioxole-4,7'-[1,2,3]triazolo[5,1-c][1,4]oxazin]-6-yl)methyl benzoate 16k
Chromatography of the crude residue over silica gel (hexane/ethyl acetate 8/2) gave the pure triazolooxazine **16k** (235 mg, 93% yield). Data for **16k**: Colourless oil, [α]_D²⁰ = -28.5 (c = 0.01, CHCl₃). ¹H-NMR (400 MHz, CDCl₃): δ 0.89 (3H, t, J = 7.2, 3×H-8'), 1.25-1.33 (4H, m, 2×H-6', 2×H-7'), 1.33 (3H, s, CH₃), 1.60 (3H, s, CH₃), 1.64 (2H, quint, J = 7.2, 2×H-5'), 2.63 (2H, td, J = 7.8, 2.4, 2×H-4'), 4.17 (1H, d, J = 12.8, H-1_a), 4.23 (1H, d, J = 12.8, H-1_b), 4.54-4.67 (3H, m, H-5, H-6_{a,b}), 4.74 (1H, d, J = 14.8, H-1'_a), 4.95 (1H, d, J = 15.2, H-1'_b), 5.14 (1H, d, J = 6.0, H-3), 5.298 (1H, dd, J = 6.0, 2.4, H-4), 7.43 (2H, t, J = 7.2, 2×H_m), 7.55 (1H, t, J = 7.2, H_p), 8.05 (2H, d, J = 7.2, 2×H_o). ¹³C-NMR (100 MHz, CDCl₃): 14.0 (C-8'), 22.4 (C-7'), 25.0 (C-4'), 25.3 (CH₃), 26.8 (CH₃), 28.6 (C-5'), 31.5 (C-6'), 62.5 (C-1'), 64.6 (C-6), 68.9 (C-1), 83.2 (C-4), 85.1 (C-5), 86.1 (C-6), 93.1 (C-2), 114.3 (C(CH₃)₂), 127.6 (C-3'), 128.3 (C_m), 129.8 (C_{ipso}), 129.8 (C_o), 133.1 (C_p), 141.7 (C-2'), 166.1 (COPh). IR (CHCl₃, cm⁻¹): 2931 (w), 1720 (s), 1450 (m), 1271 (s), 1097 (s), 1070 (m), 711 (s). HRMS required for C₂₁H₂₆N₃O₆⁺ is 416.1803, found 416.1809.

3,4-O-isopropylidene spirocyclic triazolo-oxazine nucleoside 17a
Benzoate ester **16a** was dissolved in a solution of 7 N NH₃/MeOH (0.06 M concentration) and the resulting solution was stirred for 4 h. After evaporation of the solvent under reduced pressure, the crude

product was purified on silica gel. Chromatography of the crude residue over silica gel (hexane/ethyl acetate 1/1) gave the pure spironucleoside **17a** (358 mg, 98% yield). Colourless needle crystals were obtained after recrystallisation with chloroform/hexane 1/3. Data for **17a**: Mp = 130-132 °C. [α]_D²⁰ = -120.80 (c = 0.0025, CHCl₃). ¹H-NMR (400 MHz, CDCl₃): δ 1.39 (3H, s, CH₃), 1.61 (3H, s, CH₃), 3.84 (1H, ddd, J = 11.2, 9.6, 4.0, H-6_a), 3.86-3.96 (1H, m, H-6_b), 3.98 (1H, d, J = 12.4, H-1_a), 3.21 (1H, bdd, J = 9.8, 2.4, OH), 4.31 (1H, d, J = 12.4, H-1_b), 4.55 (1H, m, H-5), 4.88 (1H, d, J = 15.2, H-1'_a), 4.97 (1H, d, J = 15.2, H-1'_b), 5.20 (1H, d, J = 6.0, H-3), 5.29 (1H, dd, J = 6.0, 2.0, H-4), 7.54 (1H, s, H-3'). ¹³C-NMR (100 MHz, CDCl₃): 24.6 (CH₃), 26.1 (CH₃), 62.4 (C-6), 63.8 (C-1'), 69.7 (C-1), 82.2 (C-4), 86.2 (C-3), 88.4 (C-5), 94.4 (C-2), 113.9 (C(CH₃)₂), 128.4 (C-3'), 132.3 (C-2'). IR (CHCl₃, cm⁻¹): 3352 (br), 2927 (w), 1095 (s), 1044 (m). HRMS required for C₁₂H₁₈N₃O₅ is 284.1241, found 284.1242.

General procedure for benzoyl and isopropyl group removal to give 18a-k¹⁴

Protected spirocyclic triazolo-oxazine nucleoside **16a-k** (0.65 mmol) was dissolved in a solution of 7 N of NH₃ in MeOH (10.8 mL) and the resulting solution was stirred at room temperature until TLC indicated the reaction was complete (ca. 4h). After evaporation of all volatiles under reduced pressure, the crude residue was dissolved in a solution of methanol/water 8/2 (26 mL) and Dowex® 50WX8 hydrogen form (3.38 g) was added in one portion. The resulting suspension was stirred vigorously for 4-6 h at 50 °C, then the resin was filtered off and washed with methanol. The filtrate was concentrated to dryness under reduced pressure to afford a crude residue which was purified by column chromatography.

(2R,3R,4S,5R)-5-(hydroxymethyl)-4,5-dihydro-3H,4'H,6'H-spiro[furan-2,7'-[1,2,3]triazolo[5,1-c][1,4]oxazine]-3,4-diol 18a

Chromatography of the crude residue over silica gel (dichloromethane/methanol 9/1) gave the pure anomeric spironucleoside **18a** (88 mg, 56% yield) as colourless syrup. Data for **18a**: [α]_D²⁰ = -38.31 (c = 0.0065, CH₃OH). ¹H-NMR (400 MHz, CD₃OD): δ 3.64 (1H, dd, J = 12.0, 6.4, H-6_a), 3.73 (1H, dd, J = 12.0, 4.0, H-6_b), 4.02 (1H, d, J = 12.4, H-1_a), 4.03-4.07 (1H, m, H-5), 4.21 (1H, d, J = 12.8, H-1_b), 4.44 (1H, d, J = 4.8, H-3), 4.62 (1H, dd, J = 6.6, 4.8, H-4), 4.73 (1H, d, J = 15.2, H-1'_a), 4.89 (1H, d, J = 15.2, H-1'_b), 7.46 (1H, s, H-3'). ¹³C-NMR (100 MHz, CD₃OD): 63.1 (C-1'), 64.0 (C-6), 70.1 (C-1), 72.6 (C-4), 77.0 (C-3), 86.6 (C-5), 94.2 (C-2), 128.9 (C-3'), 134.4 (C-2'). IR (CH₃OH, cm⁻¹): 3360 (br), 2924 (m), 1615 (br), 1093 (s), 1020 (s). HRMS required for C₉H₁₄N₃O₅⁺ is 244.0928, found 244.0928.

(2R,3R,4S,5R)-5-(hydroxymethyl)-3'-methyl-4,5-dihydro-3H,4'H,6'H-spiro[furan-2,7'-[1,2,3]triazolo[5,1-c][1,4]oxazine]-3,4-diol 18b

Chromatography of the crude residue over silica gel (dichloromethane/methanol 9/1) gave the pure spironucleoside **18b** (78 mg, 47% yield) as colourless syrup. Data for **18b**: [α]_D²⁰ = -57.1 (c = 0.01, CH₃OH). ¹H-NMR (500 MHz, CD₃OD): δ 2.26 (3H, s, 3×H-4'), 3.77 (1H, dd, J = 12.0, 6.0, H-6_a), 3.86 (1H, dd, J = 12.0, 3.5, H-6_b), 4.12

(1H, d, $J = 12.5$, H-1_a), 4.15-4.20 (1H, m, H-5), 4.31 (1H, d, $J = 12.5$, H-1_b), 4.56 (1H, d, $J = 5.0$, H-3), 4.73 (1H, dd, $J = 6.5$, 5.0, H-4), 4.80 (1H, d, $J = 15.0$, H-1'_a), 4.94 (1H, d, $J = 15.0$, H-1'_b). ¹³C-NMR (125 MHz, CD₃OD): ppm 9.5 (C-4'), 62.8 (C-1'), 64.0 (C-6), 69.8 (C-1), 72.6 (C-4), 76.9 (C-3), 86.5 (C-5), 94.2 (C-2), 130.6 (C-3'), 137.8 (C-2'). IR (CH₃OH, cm⁻¹): 3321 (br), 2993 (m), 1099 (s), 1071 (m). HRMS required for C₁₀H₁₆N₃O₅⁺ is 258.1084, found 258.1086.

(2R,3R,4S,5R)-3'-ethyl-5-(hydroxymethyl)-4,5-dihydro-3H,4'H,6'H-spiro[furan-2,7'-[1,2,3]triazolo[5,1-c][1,4]oxazine]-3,4-diol 18c

Chromatography of the crude residue over silica gel (dichloromethane/methanol 9/1) gave the pure spironucleoside **18c** (90 mg, 51% yield) as colourless syrup. Data for **18c**: [α]_D²⁰ = -34.6 (c = 0.01, CH₃OH). ¹H-NMR (400 MHz, CD₃OD): δ 1.25 (3H, t, $J = 7.6$, 3×H-4'), 2.67 (2H, q, $J = 7.6$, 3×H-3'), 3.75 (1H, dd, $J = 12.0$, 6.4, H-6_a), 3.84 (1H, dd, $J = 12.0$, 3.6, H-6_b), 4.12 (1H, d, $J = 12.4$, H-1_a), 4.13-4.18 (1H, m, H-5), 4.30 (1H, d, $J = 12.4$, H-1_b), 4.55 (1H, d, $J = 4.8$, H-3), 4.72 (1H, dd, $J = 6.4$, 4.8, H-4), 4.81 (1H, d, $J = 15.2$, H-1'_a), 4.96 (1H, d, $J = 15.2$, H-1'_b). ¹³C-NMR (100 MHz, CD₃OD): 13.6 (C-5'), 18.9 (C-4'), 63.0 (C-6), 64.0 (C-1'), 70.0 (C-1), 72.7 (C-4), 76.9 (C-3), 86.4 (C-5), 94.2 (C-2), 130.2 (C-2'), 143.6 (C-3'). IR (CH₃OH, cm⁻¹): 3392 (br), 2922 (m), 1642 (br), 1101 (s), 1033 (s), 940 (m). HRMS required for C₁₁H₁₈N₃O₅⁺ is 272.1241, found 272.1242.

(2R,3R,4S,5R)-5-(hydroxymethyl)-3'-(naphthalen-2-yl)-4,5-dihydro-3H,4'H,6'H-spiro[furan-2,7'-[1,2,3]triazolo[5,1-c][1,4]oxazine]-3,4-diol 18d

Chromatography of the crude residue over silica gel (hexane/ ethyl acetate 15/85) gave the pure spironucleoside **18d** (120 mg, 50% yield) as white solid. Data for **18d**: Mp = 101-102°C. [α]_D²⁰ = -65.5 (c = 0.01, CHCl₃). ¹H-NMR (400 MHz, CDCl₃): δ 3.89 (1H, bd, $J = 11.6$, H-6_a), 4.00 (1H, bd, $J = 11.6$, H-6_b), 4.09 (1H, br, OH), 4.12 (1H, d, $J = 12.8$, H-1_a), 4.25-4.28 (1H, m, H-4), 4.37 (1H, d, $J = 12.4$, H-1_b), 4.55 (1H, br, OH), 4.66 (1H, d, $J = 15.6$, H-1'_a), 4.75 (1H, br, H-3), 4.78 (1H, d, $J = 15.2$, H-1'_b), 5.10 (1H, br, OH), 5.26 (1H, br, H-5), 7.30 (1H, d, $J = 7.2$, H-Naph), 7.34-7.51 (3H, m, 3×H-Naph), 7.93 (3H, t, $J = 8.4$, 3×H-Naph). ¹³C-NMR (100 MHz, CDCl₃): 62.1 (C-6), 62.8 (C-1), 68.9 (C-1'), 70.9 (C-5), 76.4 (C-3), 85.2 (C-4), 93.4 (C-2), 124.9, 125.3, 126.4, 126.5, 126.9 (Naph), 127.5 (C-3'), 128.6 (Naph), 129.6 (C-2'), 130.8, 131.2, 133.9 (Naph), 140.6 (C_{ipso}-Naph). IR (cm⁻¹): 3381 (br), 2992 (w), 1211 (s), 1095 (s), 1076 (m), 777 (m), 751 (s). IR (CHCl₃, cm⁻¹): 3349 (br), 2926 (w), 1103 (s), 1035 (m), 777 (m), 757 (s). HRMS required for C₁₉H₂₀N₃O₅⁺ is 370.1397, found 370.1399.

(2R,3R,4S,5R)-5-(hydroxymethyl)-3'-phenyl-4,5-dihydro-3H,4'H,6'H-spiro[furan-2,7'-[1,2,3]triazolo[5,1-c][1,4]oxazine]-3,4-diol 18e

Chromatography of the crude residue over silica gel (hexane/ ethyl acetate 1/9) gave the pure spironucleoside **18e** (139 mg, 67% overall yield) as white foam. Data for **18e**: [α]_D²⁰ = -36.1 (c = 0.01, CHCl₃). ¹H-NMR (400 MHz, CD₃OD): δ 3.80 (1H, dd, $J = 12.0$, 6.4, H-6_a), 3.80 (1H, dd, $J = 12.4$, 3.2, H-6_b), 4.20 (1H, d, $J = 12.0$, H-1_a), 4.19-4.23 (1H, m, H-5), 4.38 (1H, d, $J = 12.4$, H-1_b), 4.64 (1H, d, $J = 5.2$, H-3), 4.73 (1H, dd, $J = 6.4$, 5.2, H-4), 5.02 (1H, d, $J = 15.2$, H-1'_a), 5.17 (1H, d, $J = 15.2$,

H-1'_b), 7.38 (1H, t, $J = 7.6$, H-7'), 7.48 (2H, t, $J = 7.6$, 2×H-6'), 7.62 (2H, d, $J = 8.0$, 2×H-5'). ¹³C-NMR (100 MHz, CD₃OD): 63.8 (C-6), 63.9 (C-1'), 69.8 (C-1), 72.7 (C-4), 77.0 (C-3), 86.6 (C-5), 94.5 (C-2), 127.3 (C-5'), 129.3 (C-2'), 130.1 (C-6'), 130.5 (C-7'), 131.5 (C-4'), 142.2 (C-3'). IR (CH₃OH, cm⁻¹): 3324 (br), 2922 (m), 1438 (s), 1101 (s), 1045 (s), 1006 (s), 943 (m). HRMS required for C₂₅H₂₆N₃O₆⁺ is 464.1816, found 464.1813.

(2R,3R,4S,5R)-3'-(4-chlorophenyl)-5-(hydroxymethyl)-4,5-dihydro-3H,4'H,6'H-spiro[furan-2,7'-[1,2,3]triazolo[5,1-c][1,4]oxazine]-3,4-diol 18f

Chromatography of the crude residue over silica gel (hexane/ ethyl acetate 1/9) gave the pure spironucleoside **18f** (145 mg, 63% overall yield) as colourless oil. Data for **18f**: [α]_D²⁰ = -31.0 (c = 0.01, CHCl₃). ¹H-NMR (500 MHz, CD₃OD): δ 3.77 (1H, dd, $J = 12.2$, 6.0, H-6_a), 3.85 (1H, dd, $J = 12.2$, 3.0, H-6_b), 4.17 (1H, d, $J = 12.5$, H-1_a), 4.15-4.19 (1H, m, H-5), 4.35 (1H, d, $J = 12.5$, H-1_b), 4.61 (1H, d, $J = 5.0$, H-3), 4.75 (1H, dd, $J = 7.0$, 5.0, H-4), 5.03 (1H, d, $J = 15.5$, H-1'_a), 5.15 (1H, d, $J = 15.5$, H-1'_b), 7.47 (2H, d, $J = 8.5$, 2×H-6'), 7.60 (2H, d, $J = 8.5$, 2×H-5'). ¹³C-NMR (125 MHz, CD₃OD): 62.4 (C-6), 63.5 (C-1'), 68.4 (C-1), 71.3 (C-4), 75.6 (C-3), 85.2 (C-5), 93.2 (C-2), 127.3 (C-5'), 128.9 (C-6'), 129.0 (C-2'), 129.4 (C-4'), 133.7 (C-7'), 139.7 (C-3'). IR (CH₃OH, cm⁻¹): 3361 (br), 2922 (m), 1636 (w), 1491 (s), 1090 (s), 1037 (s), 1002 (s), 943 (m), 831 (m). HRMS required for C₁₅H₁₇N₃O₅Cl⁺ is 354.0851, found 354.0851.

(2R,3R,4S,5R)-5-(hydroxymethyl)-3'-(4-methoxyphenyl)-4,5-dihydro-3H,4'H,6'H-spiro[furan-2,7'-[1,2,3]triazolo[5,1-c][1,4]oxazine]-3,4-diol 18g

Chromatography of the crude residue over silica gel (dichloromethane/methanol 95/5) gave the pure spironucleoside **66g** (118 mg, 52% overall yield). White needle crystals were obtained after recrystallisation with hexane/Et₂O/CH₃OH 6:3:1. Data for **66g**: Mp = 119-120°C. [α]_D²⁰ = -51.3 (c = 0.01, CHCl₃). ¹H-NMR (400 MHz, CD₃OD): δ 3.80 (1H, dd, $J = 12.4$, 6.4, H-6_a), 3.84 (3H, s, OCH₃), 3.88 (1H, dd, $J = 12.0$, 3.2, H-6_b), 4.18 (1H, d, $J = 12.4$, H-1_a), 4.18-4.22 (1H, m, H-5), 4.36 (1H, d, $J = 12.8$, H-1_b), 4.63 (1H, d, $J = 5.2$, H-3), 4.78 (1H, dd, $J = 6.4$, 5.2, H-4), 5.00 (1H, d, $J = 15.2$, H-1'_a), 5.12 (1H, d, $J = 15.2$, H-1'_b), 7.02 (2H, d, $J = 8.8$, 2×H-6'), 7.52 (2H, d, $J = 8.8$, 2×H-5'). ¹³C-NMR (100 MHz, CD₃OD): 55.8 (OCH₃), 63.9 (C-6), 64.0 (C-1'), 69.8 (C-1), 72.7 (C-4), 77.0 (C-3), 86.6 (C-5), 94.5 (C-2), 115.5 (C-6'), 123.9 (C-3'), 128.7 (C-5'), 129.0 (C-2'), 142.2 (C-4'), 161.2 (C-7'). IR (CH₃OH, cm⁻¹): 3373 (br), 2925 (m), 1615 (m), 1508 (s), 1249 (s), 1097 (s), 1038 (s), 999 (s), 943 (m), 833 (m). HRMS required for C₁₆H₂₀N₃O₆⁺ is 494.1922, found 494.1922.

(2R,3R,4S,5R)-3'-(4-fluorophenyl)-5-(hydroxymethyl)-4,5-dihydro-3H,4'H,6'H-spiro[furan-2,7'-[1,2,3]triazolo[5,1-c][1,4]oxazine]-3,4-diol 18h

Chromatography of the crude residue over silica gel (hexane/ ethyl acetate 1/9) gave the pure spironucleoside **18h** (175 mg, 80% overall yield) as white solid. Data for **18h**: [α]_D²⁰ = -40.8 (c = 0.01, CHCl₃). ¹H-NMR (400 MHz, CD₃OD): δ 3.76 (1H, dd, $J = 12.5$, 6.3, H-6_a), 3.86 (1H, dd, $J = 12.5$, 3.3, H-6_b), 4.18 (1H, d, $J = 12.2$, H-1_a), 4.16-4.20 (1H, m, H-5), 4.36 (1H, d, $J = 12.6$, H-1_b), 4.62 (1H, d, $J = 4.9$, H-3), 4.76 (1H, t,

$J = 6.2$, H-4), 5.03 (1H, d, $J = 15.3$, H-1'_a), 5.15 (1H, d, $J = 15.3$, H-1'_b), 7.21 (2H, t, $J = 8.7$, 2×H-6'), 7.60 (2H, dd, $J = 8.4$, 5.4, 2×H-5'). ¹³C-NMR (100 MHz, CD₃OD): 63.8 (C-6), 63.9 (C-1'), 69.8 (C-1), 72.7 (C-4), 77.0 (C-3), 86.6 (C-5), 94.9 (C-2), 117.0 (d, $^2J_{CF} = 22$, C-6'), 128.0 (C-4'), 129.3 (d, $^3J_{CF} = 9$, C-5'), 130.8 (C-2'), 141.5 (C-3'), 164.1 (d, $^1J_{CF} = 277$, C-7'). IR (CH₃OH, cm⁻¹): 3363 (br), 2921 (m), 1646 (m), 1506 (s), 1230 (m), 1098 (s), 1038 (s), 1004 (s), 944 (m), 838 (m). HRMS required for C₁₅H₁₇N₃O₅F⁺ is 338.1147, found 338.1147.

(2R,3R,4S,5R)-3'-(3-fluorophenyl)-5-(hydroxymethyl)-4,5-dihydro-3H,4'H,6'H-spiro[furan-2,7'-[1,2,3]triazolo[5,1-c][1,4]oxazine]-3,4-diol 18i

Chromatography of the crude residue over silica gel (hexane/ ethyl acetate 1/9) gave the pure spironucleoside **18i** (162 mg, 74% overall yield) as colourless oil. Data for **18i**: $[\alpha]_D^{20} = -46.6$ ($c = 0.01$, CHCl₃). ¹H-NMR (400 MHz, CD₃OD): δ 3.79 (1H, dd, $J = 12.0$, 6.3, H-6_a), 3.86 (1H, dd, $J = 12.0$, 3.2, H-6_b), 4.17 (1H, d, $J = 12.7$, H-1_a), 4.17-4.21 (1H, m, H-5), 4.35 (1H, d, $J = 12.6$, H-1_b), 4.63 (1H, d, $J = 4.9$, H-3), 4.77 (1H, t, $J = 6.3$, H-4), 5.02 (1H, d, $J = 15.3$, H-1'_a), 5.15 (1H, d, $J = 15.3$, H-1'_b), 7.09 (1H, td, $J = 8.3$, 2.2, H-7'), 7.33-7.40 (2H, m, H-5', H-9'), 7.46 (1H, m, H-8'). ¹³C-NMR (100 MHz, CD₃OD): 63.8 (C-6), 63.9 (C-1'), 69.8 (C-1), 72.7 (C-4), 77.0 (C-3), 86.6 (C-5), 94.6 (C-2), 113.8 (d, $^2J_{CF} = 23$, C-5'), 115.9 (d, $^2J_{CF} = 22$, C-7'), 123.0 (d, $^4J_{CF} = 3$, C-9'), 131.0 (C-2'), 132.0 (d, $^3J_{CF} = 9$, C-8'), 133.9 (d, $^3J_{CF} = 8$, C-4'), 141.0 (d, $^4J_{CF} = 2$, C-3'), 164.6 (d, $^2J_{CF} = 243$, C-6'). IR (CH₃OH, cm⁻¹): 3362 (br), 2921 (m), 1496 (m), 1102 (s), 1043 (s), 1005 (s), 943 (m), 821 (m). HRMS required for C₁₅H₁₇N₃O₅F⁺ is 338.1147, found 338.1147.

(2R,3R,4S,5R)-3'-(2-fluorophenyl)-5-(hydroxymethyl)-4,5-dihydro-3H,4'H,6'H-spiro[furan-2,7'-[1,2,3]triazolo[5,1-c][1,4]oxazine]-3,4-diol 18j

Chromatography of the crude residue over silica gel (hexane/ ethyl acetate 1/9) gave the pure spironucleoside **18j** (160 mg, 73% overall yield) as colourless oil. Data for **18j**: $[\alpha]_D^{20} = -48.2$ ($c = 0.01$, CHCl₃). ¹H-NMR (400 MHz, CD₃OD): δ 3.68 (1H, dd, $J = 12.0$, 6.3, H-6_a), 3.75 (1H, dd, $J = 12.0$, 3.3, H-6_b), 4.08 (1H, d, $J = 12.4$, H-1_a), 4.06-4.10 (1H, m, H-5), 4.25 (1H, d, $J = 12.6$, H-1_b), 4.52 (1H, d, $J = 4.9$, H-3), 4.66 (1H, t, $J = 6.0$, H-4), 4.78 (1H, d, $J = 15.4$, H-1'_a), 4.90 (1H, d, $J = 15.4$, H-1'_b), 7.11 (1H, t, $J = 10.8$, H-6'), 7.19 (1H, t, $J = 7.6$, H-8'), 7.33 (2H, dd, $J = 14.3$, 6.9, H-7'), 7.46 (1H, t, $J = 7.2$, H-8'). ¹³C-NMR (100 MHz, CD₃OD): 63.9 (C-6), 64.0 (C-1'), 70.0 (C-1), 72.7 (C-4), 77.1 (C-3), 86.6 (C-5), 94.6 (C-2), 117.0 (d, $^2J_{CF} = 24$, C-6'), 119.2 (d, $^2J_{CF} = 26$, C-4'), 126.0 (d, $^4J_{CF} = 4$, C-8'), 130.9 (d, $^5J_{CF} = 3$, C-9'), 131.8 (d, $^3J_{CF} = 10$, C-7'), 132.0 (C-2'), 137.3 (C-3'), 160.6 (d, $^2J_{CF} = 240$, C-5'). IR (CH₃OH, cm⁻¹): 3381 (br), 2922 (m), 1496 (m), 1102 (s), 1043 (s), 1004 (s), 945 (m), 823 (m). HRMS required for C₁₅H₁₇N₃O₅F⁺ is 338.1147, found 338.1147.

(2R,3R,4S,5R)-5-(hydroxymethyl)-3'-pentyl-4,5-dihydro-3H,4'H,6'H-spiro[furan-2,7'-[1,2,3]triazolo[5,1-c][1,4]oxazine]-3,4-diol 18k

Chromatography of the crude residue over silica gel (hexane/ ethyl acetate 2/8) gave the pure spironucleoside **18k** (140 mg, 69% yield) as colourless syrup. Data for **18k**: $[\alpha]_D^{20} = -47.2$ ($c = 0.01$, CHCl₃). ¹H-NMR (400 MHz, CD₃OD): δ 0.92 (3H, t, $J = 6.6$, 3×H-8'), 1.26-1.39 (4H,

m, 2×H-6', 2×H-7'), 1.63 (2H, quint, $J = 7.2$, 2×H-5'), 2.63 (2H, t, $J = 7.6$, 2×H-4'), 3.74 (1H, dd, $J = 12.0$, 6.3, H-6_a), 3.84 (1H, dd, $J = 12.0$, 3.2, H-6_b), 4.11 (1H, d, $J = 12.8$, H-1_a), 4.12-4.16 (1H, m, H-5), 4.29 (1H, d, $J = 12.6$, H-1_b), 4.54 (1H, d, $J = 4.9$, H-3), 4.70 (1H, app t, $J = 5.5$, H-4), 4.78 (1H, d, $J = 15.0$, H-1'_a), 4.89 (1H, d, $J = 13.0$, H-1'_b). ¹³C-NMR (100 MHz, CD₃OD): 14.3 (C-8'), 23.4 (C-7'), 25.5 (C-4'), 29.8 (C-5'), 32.5 (C-6'), 62.9 (C-1'), 64.0 (C-6), 70.1 (C-1), 72.6 (C-4), 77.0 (C-3), 86.2 (C-5), 94.2 (C-2), 130.4 (C-2'), 142.5 (C-3'). IR (CH₃OH, cm⁻¹): 3321 (br), 2922 (s), 1636 (br), 1456 (m), 1100 (s), 1036 (s), 941 (m). HRMS required for C₁₄H₂₄N₃O₅⁺ is 314.1716, found 314.1710.

(3aR,4R,6S,6aS)-2,2-Dimethyl-3a,6a-dihydro-4'H,6H,6'H-spiro[furo[3,4-d][1,3]dioxole-4,7'-[1,2,3]triazolo[5,1-c][1,4]oxazine]-6-carbaldehyde 19

Primary alcohol **17a** (0.97 mmol) was dissolved in dichloromethane (10 mL). Sodium bicarbonate (2.91 mmol) and Dess-Martin periodinane (1.16 mmol) were added sequentially in one portion at 0°C and the resulting mixture stirred vigorously at the same temperature until TLC analysis showed the reaction was complete (2 h). The reaction was quenched with 10% thiosulfate aq. solution (2 mL) and the mixture partitioned between saturated aq. NaHCO₃ and dichloromethane. The organic layer was washed with brine, dried over MgSO₄, filtered and concentrated to dryness under reduced pressure. Chromatography of the crude residue over silica gel (dichloromethane/methanol 95/5) gave the pure aldehyde **19** (217 mg, 80% yield) as white solid. Data for **19**: Mp = 74-75 °C. $[\alpha]_D^{25} = -60.0$ ($c = 0.01$, $l = 0.025$ dm, CHCl₃). ¹H-NMR (400 MHz, CDCl₃): δ 1.38 (3H, s, CH₃), 1.58 (3H, s, CH₃), 4.26 (1H, d, $J = 12.8$, H-1_a), 4.33 (1H, d, $J = 12.8$, H-1_b), 4.63 (1H, d, $J = 1.2$, H-3), 4.84 (1H, d, $J = 15.2$, H-1'_a), 4.98 (1H, d, $J = 6.0$, H-5), 5.08 (1H, d, $J = 15.2$, H-1'_b), 5.50 (1H, dd, $J = 5.8$, 1.3, H-4), 7.55 (1H, s, H-3'), 9.31 (1H, s, H-6). ¹³C-NMR (100 MHz, CDCl₃): 24.6 (CH₃), 26.1 (CH₃), 62.4 (C-6), 63.8 (C-1'), 69.7 (C-1), 82.2 (C-4), 86.2 (C-3), 88.4 (C-5), 94.4 (C-2), 113.9 (C(CH₃)₂), 128.4 (C-3'), 132.3 (C-2'). IR (CHCl₃, cm⁻¹): 2990 (w), 1732 (m, C=O), 1377 (m), 1211 (m), 1096 (s), 864 (m), 732 (s). HRMS required for C₁₂H₁₈N₃O₅ is 284.1241, found 284.1242.

Diethyl (2-((3aR,4R,6R,6aR)-2,2-dimethyl-3a,6a-dihydro-4'H,6H,6'H-spiro[furo[3,4-d][1,3]dioxole-4,7'-[1,2,3]triazolo[5,1-c][1,4]oxazin-6-yl)vinyl)phosphonate 20

Sodium hydride (60 % dispersion in mineral oil, 59 mg, 1.47 mmol) was suspended in dry THF (1 mL) at 0 °C under an inert atmosphere of argon. A solution of tetraethyl methylenediphosphonate (443 mg, 1.54 mmol) in dry THF (0.5 mL) was then added dropwise. The suspension was allowed to warm to room temperature and stirred for 45 min. Reaction mixture cooled down to 0°C and a solution of aldehyde **19** (197 mg, 0.70 mmol) in THF (1.5 mL) added dropwise. The resulting mixture was allowed to warm to room temperature and stirred for 2 h. The reaction mixture was treated with methanol, diluted with saturated NaHCO₃ solution and extracted with ethyl acetate. The organic phase was then washed with brine, dried over MgSO₄, filtered and concentrated to dryness under reduced pressure. Chromatography of the crude residue over silica gel (dichloromethane/methanol 96/4) gave 218 mg (80% yield) of **20** as

an inseparable 1:4 mixture of *E* and *Z* alkene isomers. Data for *Z*-isomer **20**: Colourless syrup. $[\alpha]_D^{25} = +84.0$ ($c = 0.01$, $l = 0.025$ dm, CHCl_3). $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 122-1.38 (6H, m, 6 \times H-9), 1.40 (3H, s, CH_3), 1.53 (3H, s, CH_3), 3.97-4.07 (4H, m, 4 \times H-8), 4.10-4.15 (2H, m, H-3, H-4), 4.22 (1H, d, $J = 12.8$, H-1 $_a$), 4.32 (1H, d, $J = 13.2$, H-1 $_b$), 4.82 (1H, d, $J = 15.2$, H-1' $_a$), 4.90 (1H, q, $J = 7.6$, H-5), 4.96 (1H, d, $J = 5.7$, H-7), 5.09 (1H, d, $J = 15.2$, H-1' $_b$), 5.63 (1H, dd, $J = 5.7$, 3.2, H-6), 7.53 (1H, s, H-3'). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): 16.3 (d, $^3J_{\text{CP}} = 5$, C-9), 26.0 (CH_3), 26.7 (CH_3), 61.8 (d, $^2J_{\text{CP}} = 7$, C-8 $_a$), 61.9 (d, $^2J_{\text{CP}} = 6$, C-8 $_b$), 62.4 (C-1'), 68.1 (C-1), 80.2 (C-3), 82.6 (C-5), 91.8 (C-2), 94.5 (d, $^3J_{\text{CP}} = 11$, C-5), 114.3 (C(CH_3) $_2$), 114.6 (C-7), 128.1 (C-3'), 131.1 (C-2'), 115.7 (d, $^2J_{\text{CP}} = 14$, C-6). IR (cm^{-1}): 2987 (w), 1251 (s, P=O), 1099 (s), 1026 (s, P-O-C), 968 (s), 797 (m). HRMS required for $\text{C}_{17}\text{H}_{27}\text{N}_3\text{O}_7\text{P}^+$ is 416.1587 found 416.1581.

Diethyl (2-((3*aR*,4*R*,6*R*,6*aR*)-2,2-dimethyl-3*a*,6*a*-dihydro-4'*H*,6*H*,6'*H*-spiro[furo[3,4-*d'*][1,3]dioxole-4,7'-[1,2,3]triazolo[5,1-*c'*][1,4]oxazin]-6-yl)ethyl)phosphonate **21**

In a hydrogenation vessel, vinyl phosphonate **20** (218 mg 0.52 mmol) was dissolved in methanol (4 mL) and Pd/C 10% (22 mg) was added in one portion. The reactor was purged three times with N_2 and the mixture was agitated for 5 min. After purging with H_2 three times, the reactor was pressurised to 4 bar and the resulting suspension stirred vigorously for 6 h. The catalyst was filtered, and the filtrate was evaporated to dryness. Purification of the crude product by column chromatography (silica gel, dichloromethane/ methanol 96/4) gave pure alkyl phosphonate **21** (214 mg, 94% yield) as colourless oil. Data for **21**: Colourless syrup. $[\alpha]_D^{25} = -380.0$ ($c = 0.01$, $l = 0.025$ dm, CHCl_3). $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 1.31 (6H, td, $J = 7.1$, 1.9, 6 \times H-9), 1.35 (3H, s, CH_3), 1.53 (3H, s, CH_3), 4.05-4.13 (4H, m, 4 \times H-8), 4.09 (1H, d, $J = 12.9$, H-1 $_a$), 4.21 (1H, d, $J = 12.8$, H-1 $_b$), 4.61 (1H, t, $J = 6.8$, H-5), 4.80 (1H, d, $J = 15.2$, H-1' $_a$), 5.05 (1H, d, $J = 15.1$, H-1' $_b$), 5.08-5.11 (2H, m, H-3, H-4), 7.51 (1H, s, H-3'). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): 16.4 (d, $^3J_{\text{CP}} = 6$, C-9), 22.0 (d, $^1J_{\text{CP}} = 142$, C-7), 22.1 (d, $^2J_{\text{CP}} = 4$, C-6), 24.5 (CH_3), 25.9 (CH_3), 61.5 (d, $^2J_{\text{CP}} = 6$, C-8 $_a$), 61.6 (d, $^2J_{\text{CP}} = 7$, C-8 $_b$), 62.4 (C-1'), 68.7 (C-1), 81.2 (C-3), 82.5 (d, $^3J_{\text{CP}} = 19$, C-5), 85.5 (C-4), 91.5 (C-2), 113.6 (C(CH_3) $_2$), 127.8 (C-2'), 131.2 (C-3'). IR (CH_3OH , cm^{-1}): 2983 (br), 1376 (m), 1234 (s, P=O), 1212 (s, P=O), 1098 (s, P-O-C), 1029 (P-O-C), 963 (m). HRMS required for $\text{C}_{17}\text{H}_{29}\text{N}_3\text{O}_7\text{P}^+$ is 418.1743 found 418.1736.

(2-((2*R*,3*R*,4*S*,5*R*)-3,4-Dihydroxy-4,5-dihydro-3*H*,4'*H*,6'*H*-spiro[furan-2,7'-[1,2,3]triazolo[5,1-*c'*][1,4]oxazin]-5-yl)ethyl)phosphonic acid **23**

Phosphonate nucleoside **21** (213 mg, 0.51 mmol) was dissolved in a solution of methanol/water 8/2 (20 mL) and Dowex® 50WX8 hydrogen form (2.7 g) was added in one portion. The resulting suspension was stirred vigorously for 4 h at 50°C, then the resin was filtered off and washed with methanol. The filtrate was concentrated to dryness under reduced pressure to give diol **22** as yellow oil. This crude residue was dissolved in anhydrous dichloromethane (2 mL) in 10 mL round bottom flask. 2,6-Dimethylpyridine (672 μL , 6.12 mmol) was added under inert atmosphere, followed by bromo(trimethyl)silane (538 μL , 4.08 mmol). Reaction mixture was

stirred for 2 h, then quenched with ammonium hydroxide aq. solution (5 mL). Aqueous phase was washed up with isohexane (1 mL), concentrated to dryness under vacuum to afford a crude residue which was purified by mass directed prep HPLC using a XBridge dC₁₈ 5 μ OBD 30 \times 100mm prep column. RP-HPLC was conducted an elution gradient of 1–100% B over 11.40 min, where A is H_2O in 10mM Ammonium Acetate and B is CH_3CN , to give pure phosphonate nucleoside **23** (31 mg, 12% over two steps). Data for **23**: Colourless oil. $[\alpha]_D^{25} = -44.0$ ($c = 0.01$, $l = 0.025$ dm, CHCl_3). $^1\text{H-NMR}$ (400 MHz, CD_3OD): δ 1.69-1.91 (2H, m, 2 \times H-7), 1.95-2.05 (2H, m, 2 \times H-6), 4.13 (1H, d, $J = 12.6$, H-1 $_a$), 4.28 (1H, d, $J = 12.6$, H-1 $_b$), 4.41 (1H, dd, $J = 4.6$, 3.2, H-4), 4.46 (1H, td, $J = 6.8$, 3.1, H-5), 4.82 (1H, d, $J = 15.1$, H-1' $_a$), 5.00 (1H, d, $J = 15.1$, H-1' $_b$), 5.23 (1H, d, $J = 4.3$, H-3), 7.59 (1H, s, H-3'). $^{13}\text{C-NMR}$ (100 MHz, CD_3OD): 22.6 (d, $^3J_{\text{CP}} = 3$, C-6), 23.1 (d, $^1J_{\text{CP}} = 85$, C-7), 61.6 (C-1'), 69.9 (C-1), 71.8 (C-5), 77-3 (C-3), 81.8 (d, $^4J_{\text{CP}} = 15$, C-4), 92.0 (C-2), 127.6 (C-2'), 133.5 (C-3'). $^{31}\text{P-NMR}$ (200 MHz, CD_3OD): 29.43. IR (CH_3OH , cm^{-1}): 3094 (br), 1628 (m), 1396 (s, P=O), 1066 (s, P-O-C), 915 (m). HRMS required for $\text{C}_{10}\text{H}_{17}\text{N}_3\text{O}_7\text{P}^+$ is 322.080 found 322.080.

6-*O*-Benzyl-2-deoxy-3,4-*O*-isopropylidene-2-aminomethyl- β -D-psicofuranose **24**

Lithium aluminium hydride (2.38 g, 62.6 mmol) was placed in a three necked round bottom flask equipped with thermometer, pressure equalising dropping funnel and stirrer under a nitrogen atmosphere. Anhydrous diethyl ether (50 mL) was charged at 0 °C, maintaining an internal temperature of less than 25°C. A solution of psicofuranosyl cyanide **11** (10.0 g, 31.3 mmol) in anhydrous diethyl ether (50 mL) was then added dropwise at 0 °C with careful control of the exotherm. The reaction mixture was allowed to warm to room temperature and stirred for 2 h. Excess LiAlH_4 was carefully quenched with 7 mL of AcOEt at 0 °C added dropwise (CARE: violent reaction). The following treatment with 1.0 M K_2CO_3 gave a white precipitate that was removed under filtration over celite. The filtrate was evaporated under reduced pressure to afford the crude residue as colourless oil, which was pure enough to be used immediately for the next step. Purification of the crude product by column chromatography (silica gel, ethyl acetate / methanol / ammonium hydroxide 95/4/1) gave the pure amino alcohol **24** (9.9 g, 98% yield) as a colourless oil. Data for **24**: Oil. $[\alpha]_D^{25} = +7.2$ ($c = 0.01$, $l = 0.025$, CHCl_3). $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 1.33 (3H, s, CH_3), 1.53 (3H, s, CH_3), 2.88 (1H, d, $J = 13.0$, H-1' $_a$), 3.04 (1H, d, $J = 13.0$, H-1' $_b$), 3.53 (1H, dd, $J = 10.4$, 4.3, H-6 $_a$), 3.60 (1H, dd, $J = 10.4$, 4.3, H-6 $_b$), 3.71 (1H, d, $J = 11.8$, H-1 $_a$), 3.81 (1H, d, $J = 11.8$, H-1 $_b$), 4.18 (1H, q, $J = 4.1$, H-5), 4.51 (2H, s, 2 \times H-7), 4.53-4.60 (1H, m, H-3), 4.72 (1H, dd, $J = 6.5$, 4.4, H-4), 7.25-7.36 (5H, m, 5 \times H $_{\text{Arom}}$). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): 24.5 (CH_3), 26.6 (CH_3), 45.3 (C-1'), 62.8 (C-1), 70.4 (C-6), 73.5 (C-7), 82.1 (C-4), 83.0 (C-2), 84.1 (C-5), 85.7 (C-3), 114.0 (C(CH_3) $_2$), 127.9 (C $_p$), 127.9 (C $_o$), 128.5 (C $_m$), 137.6 (C $_{\text{ipso}}$). IR (CHCl_3 , cm^{-1}): 3200 (br), 2931 (m), 1559 (m), 1381 (m), 1210 (m), 1072 (s), 866 (m). HRMS required for $\text{C}_{17}\text{H}_{26}\text{NO}_5^+$ is 324.181, found 324.180.

General procedure for sulfonyl amido ester protection:

To a stirred solution of telescoped amino alcohol **24** (1.0 eq.) in CH_2Cl_2 (0.1 M concentration), triethylamine (4.0 eq.), 4-dimethylaminopyridine (1.0 eq.) and an appropriate sulfonyl chloride (3.0 eq.) were added sequentially at 0 °C. The resulting mixture was allowed to warm to room temperature and stirred for 16 h. The reaction mixture was poured into water and the water layer was extracted with dichloromethane. The combined organic extracts were washed sequentially with 1.0 M HCl, water and brine. dried over MgSO_4 , filtered and concentrated to dryness under reduced pressure and purified by column chromatography.

6-O-Benzyl-2-deoxy-3,4-O-isopropylidene-1-O-mesyl-2-mesylaminomethyl- β -D-psicofuranose 25a¹⁶

Chromatography of the crude residue over silica gel (isohexane/ethyl acetate 1/1) gave the pure sulfonyl amidoester **25a** (979 mg, 66% o.y.) as colourless oil. Data for **25a**: Oil. $[\alpha]_{\text{D}}^{20} = +3.1$ ($c = 0.01$, CHCl_3). $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 1.32 (3H, s, CH_3), 1.51 (3H, s, CH_3), 2.74 (3H, s, $\text{NH}\text{SO}_2\text{CH}_3$), 3.05 (3H, s, SO_3CH_3), 3.29-3.30 (2H, m, $2\times\text{H-1}'$), 3.59 (1H, dd, $J = 10.4, 2.4$, H-6_a), 3.71 (1H, dd, $J = 10.4, 2.4$, H-6_b), 4.10-4.16 (1H, m, H-5), 4.31 (1H, d, $J = 10.8$, H-1_a), 4.36 (1H, $J = 10.8$, H-1_b), 4.54 (1H, d, $J = 12.0$, H-7_a), 4.59 (1H, d, $J = 12.0$, H-7_b), 4.78 (1H, d, $J = 6.0$, H-3), 5.10 (1H, t, $J = 5.2$, H-4), 7.77 (1H, dd, $J = 8.0, 4.4$, NH), 7.28-7.36 (5H, m, $5\times\text{H}_{\text{arom}}$). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): 25.2 (CH_3), 27.0 (CH_3), 37.4 (SO_3CH_3), 40.0 ($\text{NH}\text{SO}_2\text{CH}_3$), 46.9 (C-1'), 69.0 (C-1), 69.6 (C-6), 73.7 (C-7), 81.6 (C-4), 83.4 (C-3), 84.4 (C-2), 84.5 (C-5), 114.1 ($\text{C}(\text{CH}_3)_2$), 128.0 (C_p), 128.2 (C_o), 128.6 (C_m), 137.0 (C_{ipso}). IR (CHCl_3 , cm^{-1}): 3282 (br), 2936 (m), 2359 (w), 1559 (m), 1327 (m), 1175 (m), 1075 (s), 967 (m). HRMS required for $\text{C}_{19}\text{H}_{29}\text{NO}_9\text{S}_2\text{Na}^+$ is 502.1181, found 502.1176.

6-O-Benzyl-2-deoxy-3,4-O-isopropylidene-1-O-tosyl-2-tosylaminomethyl- β -D-psicofuranose 25b

Chromatography of the crude residue over silica gel (isohexane/ethyl acetate 6/4) gave the pure sulfonyl amidoester **25b** (1.22 g, 62% o.y.) as foamy gum. Data for **25b**: $[\alpha]_{\text{D}}^{20} = +3.9$ ($c = 0.01$, CHCl_3). $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 1.22 (3H, s, CH_3), 1.32 (3H, s, CH_3), 2.41 (3H, s, PhCH_3), 2.42 (3H, s, PhCH_3), 2.95 (1H, dd, $J = 12.4, 2.8$, H-1'), 2.98 (1H, dd, $J = 12.6, 10.0$, H-1'_b), 3.47 (1H, dd, $J = 10.4, 2.0$, H-6_a), 3.59 (1H, dd, $J = 10.4, 2.0$, H-6_b), 3.86-3.89 (1H, m, H-5), 4.01 (1H, d, $J = 10.4$, H-1_a), 4.10 (1H, d, $J = 10.4$, H-1_b), 4.56 (1H, d, $J = 12.4$, H-7_a), 4.62 (1H, d, $J = 12.4$, H-7_b), 4.70 (1H, d, $J = 6.0$, H-3), 4.86 (1H, t, $J = 5.6$, H-4), 6.01 (1H, dd, $J = 9.6, 2.8$, NH), 7.25 (2H, d, $J = 8.0, 2\times\text{H}_m$ Tol), 7.30 (2H, d, $J = 8.4, 2\times\text{H}_m$ Tol), 7.32-7.37 (5H, m, $5\times\text{H}_{\text{arom}}$ Ph), 7.54 (2H, d, $J = 8.0, 2\times\text{H}_o$ Tol), 7.54 (2H, d, $J = 8.4, 2\times\text{H}_o$ Tol). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): 21.5 (PhCH_3), 21.7 (PhCH_3), 25.1 (CH_3), 26.9 (CH_3), 47.4 (C-1'), 69.0 (C-6), 69.2 (C-1), 73.6 (C-7), 81.2 (C-4), 83.5 (C-3), 84.2 (C-5), 84.3 (C-2), 113.9 ($\text{C}(\text{CH}_3)_2$), 126.8 (C_o Tol), 127.8 (C_o Tol), 128.3 (C_p Ph), 128.6 (C_o Ph), 128.7 (C_m Ph), 129.8 (C_m Tol), 132.4 (C_{ipso} Tol), 136.9 (C_{ipso} Ph), 143.4 (C_p Tol), 145.0 (C_p Tol). IR (CHCl_3 , cm^{-1}): 3270 (br), 2926 (w), 2359 (w), 1189 (s), 1176 (s), 1120 (m), 988 (m). HRMS required for $\text{C}_{31}\text{H}_{37}\text{NO}_9\text{S}_2\text{Na}^+$ is 654.1807, found 654.1802.

6-O-Benzyl-2-deoxy-3,4-O-isopropylidene-1-O-nosyl-2-nosylaminomethyl- β -D-psicofuranose 25c

Chromatography of the crude residue over silica gel (isohexane/ethyl acetate 6/4) gave the pure sulfonyl amidoester **25c** (2.15 g, 97% o.y.) as white solid. Data for **25c**: Mp = 96-97 °C. $[\alpha]_{\text{D}}^{25} = +2.1$ ($c = 0.01$, CHCl_3). $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 1.29 (3H, s, CH_3), 1.43 (3H, s, CH_3), 3.52-3.61 (2H, m $2\times\text{H-6}$), 4.00 (1H, d, $J = 16.0$, H-1'_a), 4.11 (1H, d, $J = 12.0$, H-1_b), 4.19 (1H, d, $J = 16.0$, H-1'_b), 3.20-4.22 (1H, m, H-5), 4.35 (1H, d, $J = 10.5$, H-1_b), 4.51 (1H, d, $J = 11.6$, H-7_a), 4.55 (1H, d, $J = 6.2$, H-3), 4.57 (1H, d, $J = 11.6$, H-7_b), 4.66 (1H, dd, $J = 6.8, 4.1$, H-4), 7.26-7.35 (5H, m, $5\times\text{H}_{\text{arom}}$ Ph), 8.00 (2H, d, $J = 8.0, 2\times\text{H}_o$ NHNs), 8.26-8.33 (5H, m, $4\times\text{H}_{\text{arom}}$ ONs, NH), 8.31 (2H, d, $J = 8.0, 2\times\text{H}_m$ NHNs). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): 24.6 (CH_3), 25.8 (CH_3), 53.3 (C-1'), 69.3 (C-1), 70.3 (C-6), 73.6 (C-7), 82.0 (C-2), 82.6 (C-4), 82.9 (C-5), 84.4 (C-3), 115.5 ($\text{C}(\text{CH}_3)_2$), 124.1 (C_o NHNs), 124.2 (C_m ONs), 128.0 (C_o Ph), 128.1 (C_o ONs), 128.6 (C_p Ph), 129.5 (C_o NHNs), 130.5 (C_m Ph), 137.4 (C_{ipso} Ph), 141.2 (C_{ipso} NHNs), 144.2 (C_{ipso} ONs), 150.7 (C_p NHNs), 150.9 (C_p ONs). IR (CHCl_3 , cm^{-1}): 3108 (w), 2357 (w), 1532 (s, N-O), 1350 (s, N-O), 1172 (m), 1082 (m), 978 (w). HRMS required for $\text{C}_{23}\text{H}_{27}\text{N}_2\text{O}_8\text{S}^+$ is 491.1488, found 491.1482.

General procedure for Sulfoazetidine Spirocyclization

Sodium hydride (60 % dispersion in mineral oil, 10 eq.) was placed in a three necked round bottom flask equipped with thermometer, stirrer bar and pressure equalising dropping funnel under a nitrogen atmosphere. It was then charged with anhydrous DMF (0.05M) at 0 °C, maintaining an internal temperature less than 25 °C. A solution of suitable sulfonyl amidoester **25a-c** in anhydrous DMF (0.05 M) was then added dropwise over 15 min and stirred for a further 15 min at 0 °C with careful control of exotherm. The reaction was allowed to warm to room temperature and stirred until TLC analysis showed complete reaction (16-48 h). The excess of NaH was quenched by careful dropwise addition of methanol at 0 °C maintaining an internal temperature of less than 25 °C. The suspension was then diluted with water and extracted with diethylether. The combined organic extracts were washed with saturated aq. NH_4Cl solution, dried over MgSO_4 , filtered and concentrated to dryness under reduced pressure and purified by column chromatography.

(6R,7S,8R)-2-Aza-6-benzyloxymethyl-7,8-

(dimethylmethylenedioxy)-2-N-mesyl-5 oxaspiro[3.4]-octane 26a¹⁶

Chromatography of the crude residue over silica gel (isohexane/ethyl acetate 7/3) gave the pure mesyl spiroazetidine **26a** (485 mg, 63%) as colourless oil. Data for **26a**: Oily. $[\alpha]_{\text{D}}^{20} = -63.7$ ($c = 0.01$, CHCl_3). $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 1.36 (3H, s, CH_3), 1.42 (3H, s, CH_3), 2.85 (3H, s, SO_2CH_3), 3.48 (1H, dd, $J = 10.0, 2.5$, H-6_a), 3.52 (1H, dd, $J = 10.0, 2.5$, H-6_b), 3.57 (1H, d, $J = 8.8$, H-1'_a), 3.59 (1H, dd, $J = 10.0, 2.5$, H-6_b), 3.67 (1H, d, $J = 8.8$, H-1'_b), 3.92 (1H, d, $J = 8.8$, H-1_a), 4-20-4.23 (1H, m, H-5), 4.21 (1H, d, $J = 8.8$, H-1_b), 4.40 (1H, d, $J = 12.0$, H-7_a), 4.50 (1H, d, $J = 11.6$, H-7_b), 4.73 (1H, d, $J = 6.0$, H-3), 4.79 (1H, d, $J = 6.0$, H-4), 7.25-7.38 (5H, m, $5\times\text{H}_{\text{arom}}$). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): 25.2 (CH_3), 27.0 (CH_3), 37.4 (SO_3CH_3), 40.0 ($\text{NH}\text{SO}_2\text{CH}_3$), 46.9 (C-1'), 69.0 (C-1), 69.6 (C-6), 73.7 (C-7), 81.6 (C-4), 83.4 (C-3), 84.4 (C-2), 84.5 (C-5), 114.1 ($\text{C}(\text{CH}_3)_2$), 128.0 (C_p), 128.2 (C_o), 128.6 (C_m), 137.0 (C_{ipso}).

IR (CHCl₃, cm⁻¹): 2935 (w), 2359 (w), 1336 (m), 1130 (s), 1070 (m), 960 (w). HRMS required for C₁₈H₂₅NO₆SN⁺ is 406.1295, found 406.1295.

(6R,7S,8R)-2-Aza-6-benzyloxymethyl-7,8-(dimethylmethylenedioxy)-2-N-tosyl-5 oxaspiro[3.4]-octane 26b

Chromatography of the crude residue over silica gel (isohexane/ethyl acetate 7/3) gave the pure tosyl spiroazetidine **26b** (243 mg, 54%) as colourless oil. Data for **26b**: Oily. [α]_D²⁰ = -70.4 (c = 0.01, CHCl₃). ¹H-NMR (400 MHz, CDCl₃): δ 1.29 (3H, s, CH₃), 1.36 (3H, s, CH₃), 2.45 (3H, s, PhCH₃), 3.40 (2H, s, 2×H-6), 3.54 (1H, d, *J* = 9.6, H-1'_a), 3.57 (1H, d, *J* = 9.7, H-1'_b), 3.67 (1H, d, *J* = 8.8, H-1_a), 4.10-4.14 (2H, m, H-5, H-1_b), 4.37 (1H, d, *J* = 11.7, H-7_a), 4.43 (1H, d, *J* = 11.7, H-7_b), 4.49 (1H, d, *J* = 5.9, H-3), 4.70 (1H, d, *J* = 5.9, H-4), 7.22-7.26 (2H, m, 5×H_m Tol), 7.32-7.39 (5H, m, 2×H_{arom} Ph), 7.68 (2H, d, *J* = 7.9, H_o Tol). ¹³C-NMR (100 MHz, CDCl₃): 21.6 (PhCH₃), 25.0 (CH₃), 26.4 (CH₃), 57.3 (C-1), 64.0 (C-1'), 71.5 (C-6), 73.9 (C-7), 80.9 (C-2), 82.9 (C-4), 83.8 (C-5), 85.5 (C-3), 112.4 (C(CH₃)₂), 128.1 (C_p Ph), 128.2 (C_o Ph), 128.4 (C_o Tol), 128.6 (C_m Tol), 129.7 (C_m Ph), 131.7 (C_p Tol), 137.0 (C_{ipso} Ph), 143.9 (C_{ipso} Tol). IR (CHCl₃, cm⁻¹): 2937 (w), 2359 (w), 1344 (m), 1127 (s), 1090 (m). HRMS required for C₂₄H₂₉NO₆SN⁺ is 482.1613, found 482.1608.

(6R,7S,8R)-2-Aza-6-benzyloxymethyl-7,8-(dimethylmethylenedioxy)-2-N-nosyl-5 oxaspiro[3.4]-octane 26c

Chromatography of the crude residue over silica gel (isohexane/ethyl acetate 7/3) gave the pure nonyl spiroazetidine **26c** (84 mg, 12%) as colourless oil. Data for **26c**: Oily. [α]_D²⁵ = -67.2 (c = 0.01, l = 0.025 dm, CHCl₃). ¹H-NMR (400 MHz, CDCl₃): δ 1.28 (3H, s, CH₃), 1.36 (3H, s, CH₃), 2.45 (3H, s, PhCH₃), 3.41-3.47 (2H, m, 2×H-6), 3.57 (1H, d, *J* = 9.3, H-1'_a), 3.62 (1H, d, *J* = 9.3, H-1'_b), 3.75 (1H, d, *J* = 9.1, H-1_a), 4.12 (1H, t, *J* = 2.1, H-5), 4.20 (1H, d, *J* = 9.1, H-1_b), 4.38 (1H, d, *J* = 12.0, H-7_a), 4.42 (1H, d, *J* = 12.0, H-7_b), 4.43 (1H, d, *J* = 5.9, H-3), 4.70 (1H, d, *J* = 6.0, H-4), 7.21-7.28 (2H, m, 2×H_o Ph), 7.35-7.42 (3H, m, 2×H_m, H_p Ph), 7.94 (2H, d, *J* = 7.9, H_o Ns), 8.37 (2H, d, *J* = 7.9, H_o Ns). ¹³C-NMR (100 MHz, CDCl₃): 25.0 (CH₃), 26.4 (CH₃), 57.8 (C-1), 64.7 (C-1'), 71.6 (C-6), 74.0 (C-7), 81.2 (C-2), 83.1 (C-4), 83.8 (C-5), 85.5 (C-3), 112.6 (C(CH₃)₂), 124.2 (C_m Ns), 128.2 (C_o Ph), 128.3 (C_p Ph), 128.6 (C_m Ph), 129.4 (C_o Ns), 136.8 (C_{ipso} Ph), 141.2 (C_{ipso} Ns), 150.0 (C_p Ns). IR (CHCl₃, cm⁻¹): 2932 (w), 2157 (w), 1550 (s, N-O), 1349 (s, N-O), 1163 (s), 737 (s). HRMS required for C₂₃H₂₇N₂O₈S⁺ is 491.1488, found 491.1482.

(6R,7S,8R)-2-Aza-6-benzyloxymethyl-7,8-(dimethylmethylenedioxy)-5-oxa-2-azaspiro[3.4]-octane 28

To a stirred suspension of K₂CO₃ (56 mg, 0.41 mmol) in CH₃CN (1 mL) was added a solution of *N*-nosyl spiroazetidine **26c** (100 mg, 0.20 mmol) in CH₃CN (1 mL) under N₂ atmosphere followed by thiophenol (21 μ L, 0.61 mmol). The reaction mixture was stirred for 18 h, diluted with ethyl acetate, washed with brine, dried over MgSO₄, filtered and concentrated to dryness under reduced pressure. Purification was performed by mass directed prep HPLC using a XBridge dC₁₈ 5 μ OBD 30×100mm prep column. RP-HPLC was conducted with an elution gradient of 1–100% B over 11.40 min, where A is H₂O in 10mM Ammonium Acetate and B is CH₃CN and gave pure azetidine

spironucleoside **27** (29 mg, 48%). Data for **27**: Oily. [α]_D²⁵ = -56.0 (c = 0.01, l = 0.025 dm, CH₃OH). ¹H-NMR (400 MHz, CDCl₃): δ 1.35 (3H, s, CH₃), 1.41 (3H, s, CH₃), 3.44 (1H, dd, *J* = 10.2, 3.0, H-6_a), 3.48 (1H, dd, *J* = 10.2, 3.0, H-6_b), 3.59 (1H, d, *J* = 10.1, H-1'_a), 3.76 (1H, d, *J* = 10.3, H-1'_b), 3.87 (1H, d, *J* = 10.3, H-1_a), 4.08 (1H, d, *J* = 10.2, H-1_b), 4.19 (1H, t, *J* = 2.6, H-5), 4.39 (1H, d, *J* = 11.8, H-7_a), 4.48 (1H, d, *J* = 11.8, H-7_b), 4.76 (1H, d, *J* = 6.0, H-3), 4.82 (1H, d, *J* = 6.0, H-4), 5.04 (1H, br, NH), 7.22-7.38 (5H, m, 5×H_{arom}). ¹³C-NMR (100 MHz, CDCl₃): 25.1 (CH₃), 26.4 (CH₃), 52.6 (C-1'), 59.2 (C-1), 71.5 (C-6), 73.9 (C-7), 83.1 (C-4), 83.9 (C-5), 84.5 (C-2), 85.4 (C-3), 112.5 (C(CH₃)₂), 128.0 (C_o), 128.1 (C_p), 128.6 (C_m), 137.0 (C_{ipso}). IR (CH₃OH, cm⁻¹): 2936 (m), 1556 (m), 1380 (s), 1280 (s), 1160 (s), 1051 (s), 871 (s). HRMS required for C₇H₁₄NO₄⁺ is 306.170 found 306.170.

General procedure for O-deprotection

Isopropylidene sulfoazetidine spironucleoside **26a-b** was dissolved in a solution of methanol/water 8/2 (0.025 M concentration). Dowex® 50WX8 hydrogen form (3.4 g/mol) was added in one portion and the resulting suspension was stirred vigorously at 50 °C until total consumption of the starting material (4-6 h), then the resin was filtered off and washed with methanol. The filtrate was evaporated under reduced pressure to afford crude benzyl ether spironucleoside crude as pale yellow oil. Residue was dissolved in methanol (0.1 M) and charged into hydrogenation vessel. Palladium on activated charcoal 10wt.%, (10% of weight with respect of **26a-b**) was added in one portion. The reactor was purged three times with N₂ and the mixture was agitated for 5 min. After purging with H₂ a further three times, the reactor was pressurised to 4 bar and the resulting suspension was stirred vigorously until total consumption of the starting material (ca. 22 h). The catalyst was filtered off, and the filtrate was evaporated to dryness.

(6R,7S,8R)-2-Aza-7,8-dihydroxy-6-hydroxymethyl-2-N-mesyl-5-oxaspiro[3.4]octane 27a

Purification of the crude product by column chromatography (silica gel, dichloromethane/ methanol 94/6) gave the title compound **27a** (120 mg, 94% yield) as colourless oil. [α]_D²⁵ = -32.0 (c = 0.01, l = 0.025 dm, CH₃OH). ¹H-NMR (400 MHz, CD₃OD): δ 2.94 (3H, s, SO₂CH₃), 3.54 (1H, dd, *J* = 12.0, 4.0, H-6_a), 3.67 (1H, dd, *J* = 12.0, 3.5, H-6_b), 3.80 (1H, dd, *J* = 9.0, 1.0, H-1_a), 3.85-3.88 (1H, m, H-5), 3.90 (1H, dt, *J* = 9.0, 1.0, H-1'_a), 3.96 (1H, dd, *J* = 9.0, 0.8, H-1'_b), 3.98-4.06 (2H, m, H-3, H-4), 4.31 (1H, dd, *J* = 9.0, 1.0, H-1_b). ¹³C-NMR (125 MHz, CD₃OD): 34.3 (SO₂CH₃), 59.2 (C-1), 61.6 (C-1'), 62.9 (C-6), 72.4 (C-3), 75.7 (C-4), 80.1 (C-2), 85.6 (C-5). IR (CH₃OH, cm⁻¹): 3422 (br), 2963 (w), 1397 (w), 1262 (s), 1092 (s), 1024 (s), 801 (s).

(6R,7S,8R)-2-Aza-7,8-dihydroxy-6-hydroxymethyl-2-N-mesyl-5-oxaspiro[3.4]octane 27b.

Purification of the crude product by column chromatography (silica gel, dichloromethane/ methanol 95/5) gave the title compound **27b** (215 mg, 52% yield) as amorphous solid. White needle crystals were obtained after recrystallisation with ethyl acetate. Mp = 96-97 °C. [α]_D²⁵ = -40.0 (c = 0.01, l = 0.025 dm, CH₃OH). ¹H-NMR (400 MHz, CD₃OD): δ 2.46 (3H, s, PhCH₃), 3.44 (1H,

dd, $J = 12.2$, 4.1, H-6_a), 3.53 (1H, d, $J = 8.6$, H-1_a), 3.57 (1H, dd, $J = 12.2$, 3.1, H-6_b), 3.67 (1H, d, $J = 8.8$, H-1'_a), 3.71 (1H, d, $J = 8.8$, H-1'_b), 3.73-3.77 (1H, m, H-5), 3.87 (1H, d, $J = 4.7$, H-3), 3.94 (1H, dd, $J = 5.7$, 4.7, H-4), 4.17 (1H, d, $J = 8.6$, H-1_b), 7.46 (2H, d, $J = 8.0$, 2×H_m), 7.72 (2H, d, $J = 8.3$, 2×H_o). ¹³C-NMR (100 MHz, CD₃OD): 22.1 (PhCH₃), 60.0 (C-1), 62.7 (C-1'), 63.2 (C-6), 72.6 (C-4), 76.3 (C-3), 80.2 (C-2), 85.6 (C-5), 130.2 (C_o), 131.5 (C_m), 132.8 (C_p), 146.3 (C_{ipso}). IR (CH₃OH, cm⁻¹): 3347 (br), 2928 (w), 1332 (w), 1157 (m), 1090 (s), 1017 (s), 814 (m). HRMS required for C₁₄H₂₀NO₆S⁺ is 330.101 found 330.100.

Crystallography

Crystal structures at 150 K for **17a** and **27b** were obtained using an Oxford Diffraction Gemini single-crystal diffractometer equipped with an Oxford Instruments Cryojet cooling device. Whilst a satisfactory solution and refinement of the structure of **17a** was achieved, and the structure of **27b** easily solved, refinement of the latter did not progress to a satisfactory conclusion. Diffraction data for **27b** were therefore recollected at 150K at the EPSRC UK National Crystallography Service at the University of Southampton and the structure then refined satisfactorily as a 4-component twin. Both crystal structures have been deposited with the CCDC as reference numbers 1840501 (**17a**) and 1840502 (**27b**).

Viruses and cells.

The A59 strain of *Mouse hepatitis virus* was used in all experiments. 17Cl-1 mouse lung fibroblast cells were grown in complete growth medium consisting of Dulbecco's modified Eagle medium (DMEM; Invitrogen) supplemented with 10% heat-inactivated foetal bovine serum (FBS; Invitrogen), penicillin and streptomycin (Invitrogen), and nonessential amino acids (NEAA; Invitrogen).

MTT Toxicity assay.

MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] assays were used to measure cell viability of experimentally treated cells. 17Cl-1 cells in complete growth medium were treated with specified concentrations of test substance in a total volume of 2 ml and plated in 96-well plates at a density of about 50% confluence. After 72 h of treatment, 5-mg/ml MTT (Sigma) was added to each well in a six-well plate. Cells were then incubated at 37°C for 1 h, when blue coloration appeared in the majority of untreated control cells indicating that the MTT had been reduced to the insoluble compound formazan. Assays were protected from light during MTT treatment. The medium was then aspirated and replaced with 1 ml of dimethyl sulfoxide to solubilize the cells. Absorbance at 540 nm was read in a Molecular Devices plate reader and analysed by the SOFTmax program.

Virus growth inhibition assay.

17Cl-1 cells were seeded at a density of 2×10⁵ cells per well of a 12-well tissue culture plate and allowed to adhere overnight at 37°C and 5% CO₂. Cells were pre-treated for 3h with 2 ml of complete medium containing 100 µl of test compounds dissolved in a vehicle of 90% water and 10% dimethyl sulfoxide or vehicle alone. After the pre-treatment, cells were inoculated at a multiplicity of about 10 PFU/cell

with MHV-A59. After 1 h cells were rinsed three times with warm phosphate-buffered saline to remove any unbound virus, then culture medium containing the same treatment as before was reapplied. 14h after inoculation, cell culture medium was collected and stored for virus quantification.

Virus quantification by plaque assay.

17Cl-1 cells were seeded in 12-well tissue culture plates at 2×10⁵ cells per well and allowed to adhere overnight at 37°C, 5% CO₂. Culture medium was removed and replaced with 0.5 ml of serial dilutions of inoculum in culture medium, then incubated at 37°C for 1 h. Inocula were left in place, and cells were overlaid with 0.7% agarose (Doc Frugal) in DMEM supplemented with 2% serum (final concentration) and incubated at 37°C with 5% CO₂ for 2 days. Cells were fixed with 25% formaldehyde in phosphate-buffered saline; agarose plugs were removed, and cells were stained with 0.1% crystal violet to visualize viral plaques.

Syncytium inhibition assay.

17Cl-1 cells were seeded in 25-cm² flasks, pre-treated, and inoculated as before. Infection was allowed to proceed for 24 h before medium was removed, and cells were fixed and stained as before. Multinucleate cells, including virus-induced syncytia, were observed and photographed as described above. Multinucleate cells falling within a 4-mm² window were counted manually for each flask. Statistical significance of differences between syncytium formation after control or experimental treatment was tested by using a two-sample t test in InStat 3.0 (Graphpad).

Conflicts of Interest

There are no conflicts to declare

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